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# **ENDOSCOPIC THERAPY IN EXTRAHEPATIC BILIARY STRICTURES**

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ACADEMIC DISSERTATION

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*To my precious family*

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## LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following publications, which in the text are referred to by their Roman numerals:

- I. Haapamäki C, Udd M, Halttunen J, Lindström O, Mäkisalo H, Kylänpää L. Endoscopic treatment of anastomotic biliary complications after liver transplantation using removable, covered, self-expandable metallic stents. *Scandinavian Journal of Gastroenterology* 47: 116–121, 2012.
- II. Haapamäki C, Seppänen H, Udd M, Juuti A, Halttunen J, Kiviluoto T, Sirén J, Mustonen H, Kylänpää L. Preoperative biliary decompression preceding pancreaticoduodenectomy with plastic or self-expandable metallic stent. *Scandinavian Journal of Surgery* 104: 79-85, 2015; first published on July 15, 2014 DOI:10.1177/1457496914543975.
- III. Haapamäki C, Kylänpää L, Udd M, Lindström O, Grönroos J, Saarela A, Mustonen H, Halttunen J. Randomized multicenter study of multiple plastic stents vs. covered self-expandable metallic stents in the treatment of biliary stricture in chronic pancreatitis. *Endoscopy* 47(07): 605-610, 2015.
- IV. Haapamäki C, Udd M, Kylänpää L. Benign biliary strictures treated with fully covered metallic stents in patients with surgically altered anatomy using double balloon enteroscopy. *Journal of Laparoendoscopic & Advanced Surgical Techniques* 25(0) DOI: 10.1089/lap.2015.0417, 2015.

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## ABBREVIATIONS

AFOS	alkaline phosphatase
AS	anastomotic stricture
ASA	American Society of Anesthesiologists' Physical Status Classification
BBS	benign biliary stricture
BDS	biodegradable stent
CBD	common bile duct
CC	choledocho-choledochal
CCA	cholangiocarcinoma
CCI	Charlson Comorbidity Index
CRP	C-reactive protein
cSEMS	covered self-expandable metallic stent
CT	computed tomography
DAE	device-assisted enteroscopy
DBE	double-balloon enteroscopy/ -e
ERC(P)	endoscopic retrograde cholangio(pancreatography)
ESGE	European Society of Gastrointestinal Endoscopy
EUS	endoscopic ultrasound
fcSEMS	fully covered self-expandable metallic stent
Fr	French; 1 Fr= $\frac{1}{3}$ mm
GI	gastrointestinal
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HJ	hepaticojejunostomy
IQR	interquartile range
LT	liver transplant/-ation
MBS	malignant biliary stricture
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NAS	non-anastomotic stricture
NEPS	non-expandable plastic stent
PBD	preoperative biliary drainage
PCL	poly-capro-lactone
pcSEMS	partly covered self-expandable metallic stent
PD	pancreaticoduodenectomy



PDX	polydioxanone
PEG	percutaneous endoscopic gastrostomy
PEP	post-ERCP pancreatitis
PGA	polyglycolide
PLA	polylactic acid
PSC	primary sclerosing cholangitis
PTC	percutaneous transhepatic cholangiography
PTBD	percutaneous transhepatic biliary drainage
PTFE	polytetrafluoroethylene
RCT	randomized controlled trial
RFA	radiofrequency ablation
RR	relative risk
RYGB	Roux-en-Y gastric bypass
SBE	Single-balloon enteroscopy/ -e
SD	standard deviation
SEMS	self-expandable metallic stent
TP	total pancreatectomy
UBO	unstented patients with biliary obstruction
UNO	unstented patients with no biliary obstruction
US	ultrasound
uSEMS	uncovered self-expandable metallic stent

## ABSTRACT

Extrahepatic biliary strictures are mainly managed using stents when treated endoscopically. At present, the main stent types in clinical practice are non-expandable plastic stents (NEPS) and self-expandable metallic stents (SEMS), with an up to tenfold cost for the latter. In current praxis, SEMS are widely used for palliative management of malignant biliary strictures as they have longer patency. The role of SEMS in preoperative stenting and the management of benign biliary strictures (BBS) are unclear.

The main purpose of this study was to describe the therapy outcome of metallic stenting in anastomotic strictures of liver transplanted (LT) patients, to compare stenting with NEPS and SEMS preoperatively preceding pancreaticoduodenectomy and in BBS caused by chronic pancreatitis (CP) and, finally, to describe stenting of BBS using covered SEMS (cSEMS), a new technique that has not previously been possible, particularly in patients with surgically altered anatomy.

The therapy outcome of 17 LT patients with anastomotic biliary stricture or leakage treated with cSEMS was retrospectively analyzed in the piloting study (I). In Study II, the stent success and the surgical outcome of 191 patients preoperatively stented, with either NEPS or SEMS who had undergone pancreaticoduodenectomy or total pancreatectomy were analyzed in a retrospective manner. As a supplementary group, 166 preoperatively unstented and 9 percutaneously, transhepatically drained patients were evaluated concerning surgical outcome. A prospective, randomized, controlled trial was conducted in Study III to compare multiple NEPS with cSEMS therapy in biliary strictures caused by CP, with 30 patients in each group. Study IV presented three patient cases along with detailed description of equipment, devices, technique and outcome, when using cSEMS for BBS in patients with altered anatomy.

The median stenting time for the LT patients (I) was 6.8 months (0.9–10.1). The overall stent migration rate was 24%; 100% for Wallstent™ (n=3), 4% for Allium™ (n=13) and 0% for a custom-made Micro-Tech (n=2) stent. There were two recurrences, but eventual stricture resolution was achieved in all patients after restenting. The median follow-up was 21.7 months (6.6–32.0) after stent removal.

For the preoperatively stented patients (II), the stent failure rate was 7.4% (95% confidence interval [CI] 4.0%–12.3%) for NEPS and 3.4% (95% CI 0.1%–17.7%) for SEMS, ( $p=0.697$ ). Among the NEPS stented patients, 45% with a pre-stent bilirubin level exceeding 50  $\mu\text{mol/l}$  reached a preoperative level of 20  $\mu\text{mol/l}$  or less, compared with 26% in the SEMS group ( $p=0.110$ ). A level lower than 50  $\mu\text{mol/l}$  was achieved by 80% of patients in the NEPS group and by 61% in the SEMS group ( $p=0.058$ ). The bile juice bacterial scores did not differ between the differently stented patients,

but a statistically significant difference was found when the proportion of sterile bile juices in unstented patients with biliary obstruction (100%; n= 7/7) was compared with that of the stented patients (1%; n=1/155;  $p<0.001$ ). Postoperative infection complications did not show any significant difference when comparing these stented and unstented groups with biliary obstruction. However, the number of unstented patients with biliary obstruction was very small. Overall postoperative infections, postoperative pancreatic fistulas or reoperations showed no significant difference between study groups.

For the patients with CP and BBS (III), the median follow-up was 40 months (range 1–66 months). The stricture-free success rate at two years was 90% (95% CI 72%–97%) in the NEPS group and 92% (95%CI 70%–98%) in the cSEMS group ( $p=0.405$ ). One late recurrence in the NEPS group, 50 months after stent removal, decreased the success rate to 72% (95% CI 27%–92%). The migration rate was 10% in the NEPS group and 7% in the cSEMS group ( $p=1.000$ ).

Three patients with altered anatomy and BBS successfully received an endoscopically deployed cSEMS, two of them utilizing the rendezvous technique, as the percutaneous transhepatic cholangiogram (PTC) route was available when the procedure was started (IV).

In conclusion, endoscopic therapy with cSEMS is safe and efficient both regarding anastomotic complications after LT and CP-induced BBS. Progressive stenting with NEPS is a good alternative in BBS caused by CP, however, with impaired patient comfort. In ordinary preoperative stenting, SEMs do not seem to offer any advantage over NEPS. In patients with altered anatomy, endoscopic deployment of cSEMS in BBS has become possible, as equipment and devices have evolved.

# 1. INTRODUCTION

Traditionally biliary strictures have been treated either surgically or by percutaneous transhepatic biliary drainage (PTBD). As the endoscopic devices have evolved, endoscopic methods have increasingly been utilized.

In stent therapy, non-expandable plastic stents (NEPS) were the only ones available for some time. In the treatment of biliary strictures the limited diameter (up to 11.5 Fr; 3.8 mm) of NEPS in single-stent therapy is associated with stricture recurrence. This can be overcome with balloon dilation and multiple stenting, requiring, however, several successive endoscopic retrograde cholangiopancreatography (ERCP) procedures. When self-expandable metallic stents (SEMS) with a larger diameter (expanding to 8–12 mm) became available, their use was limited to malignant strictures since they could not be removed due to tissue imbedding. Later, covered metallic stents (cSEMS) enabling stent removal were developed. These can be partly covered (pcSEMS) or fully covered self-expandable metallic stents (fcSEMS). It is still not known whether stenting with multiple plastic stents or cSEMS is preferable in benign biliary strictures.

Biliary reconstruction in liver transplants mainly consists of choledocho-choledochal (CC) anastomoses in patients receiving the transplant for indications other than primary sclerosing cholangitis (PSC), biliary atresy, and Caroli disease when reconstruction with a hepaticojejunostomy (HJ) most often is used. The CC anastomosis enables traditional therapeutic ERCP, in contrast to a HJ with Roux-en-Y reconstruction, which was endoscopically inaccessible until only a few years ago.

Preoperative biliary drainage (PBD) has been used prior to pancreaticoduodenectomy in jaundiced patients, as obstructive jaundice is associated with impaired hepatic function, coagulation disturbances, and development of cholangitis. Recent studies have, however, shown routine PBD to offer no benefit over early surgery (within two weeks) without PBD(1-3). Since early surgery is not always possible, PBD still plays a role. Preoperative biliary drainage using SEMS has been suggested to drain the biliary tree more efficiently than NEPS and also to correlate with a lower postoperative complication rate. As the cost for SEMS is significantly higher than that for plastic stents, an evaluation of this kind of temporary preoperative use is needed.

After total or partial gastrectomy with Billroth II or Roux-en-Y reconstruction, pancreaticoduodenectomy, some duodenal or choledochal injuries, LT with HJ and Roux-en-Y gastric bypass (RYGB) for morbid obesity, the anatomy is surgically altered, making traditional ERCP with a duodenoscope difficult and often impossible.

The percutaneous transhepatic cholangiogram route was the only access to the biliary tree until only a few years ago, when device-assisted endoscopy with either double-balloon, single-balloon, or spiral enteroscopy enabled endoscopic access. Even though the papilla or HJ can be reached, the length of the endoscope and/or the narrow diameter of the working channel limit the use of traditional ERCP accessories. However, the equipment is continuously evolving.

## **2. REVIEW OF THE LITERATURE**

### **2.1 ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY**

Since McCune first described ERCP in 1968, it has evolved tremendously. There are still indications (i.e. PSC) for pure diagnostic ERCP, but the emphasis lies on therapeutic procedures. The diagnostic dimension has mainly been replaced by various imaging modalities such as magnetic resonance cholangiopancreatography (MRCP). Extrahepatic biliary strictures are most often handled using stents when managed endoscopically (4).

### **2.2 STENT TYPES IN BILIARY STENTING**

#### **2.2.1 NON-EXPANDABLE PLASTIC STENTS**

Most plastic stents consist of polyurethane, Teflon™, or polyethylene (5). The shape of biliary NEPS is often slightly curved to obviate migration and to suit the common bile duct (CBD) contour. There can be side holes to enable drainage in cases of stent tip imbedding in the CBD or the intestinal wall. However, side holes are suspected of enhancing stent clogging, which is why stents with antimigratory side flaps lacking side holes (Tannenbaum™ stent) have been developed. Polyethylene models appear to allow obstruction relief more often than Tannenbaum™ or Amsterdam type Teflon™ stents, and the European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend the avoidance of Teflon™ stents when polyethylene stents are available. Occluded NEPS should be replaced (6).

The external diameters for biliary NEPS are 7.0, 8.5, 10.0, and 11.5 Fr and the standard lengths range between 5 and 18 cm. Some manufacturers offer the possibility for longer, custom-made stents when needed. A larger diameter is difficult to introduce, however, as the diameter of the working channel on standard duodenoscopes is 4.2 mm (5). Nevertheless, larger stenting diameters can be achieved by placing multiple stents side by side after balloon dilation. Post-cholecystectomy bile duct strictures treated with multiple NEPS in a study with a small sample (n=20), revealed that hyperplastic tissue on the stricture site, seen on cholangioscopy when the stent therapy ended, predicted recurrence, contrary to minor strictures with a fibrous ring or no findings at all (7).

Migration rates of 5.9% for distal and 4.9% for proximal migration have been presented for NEPS. Plastic stents migrate more frequently in BBS than in malignant biliary strictures (MBS), and single stents more often than multiple stents. Distally migrated NEPS are usually spontaneously eliminated, although intestinal perforation is a possible, albeit infrequent, complication (8).

## **2.2.2 SELF-EXPANDABLE METALLIC STENTS**

The benefit of SEMS in comparison with NEPS is their expansion to a much larger diameter, enabling longer patency. The cost for SEMS is a major disadvantage, as it is about ten times that of NEPS. There are numerous types of stents within the SEMS group, differing in properties such as design at the ends, shortening ratio, radiopacity, covering, radial and axial force, flexibility, mesh cell size, anchoring mechanisms, and, consequently, price (5, 9). In vitro measurements have revealed markedly different results in radial and axial force between otherwise identical covered and uncovered SEMS (9).

The stent design for SEMS intended for extrahepatic bile duct differs from that of hilar SEMS. Metallic stents with a central portion with a larger open cell size facilitate stenting of the contralateral bile duct with stent-in-stent placement. Hilar stents with smaller cell size reducing tumor ingrowth need side-by-side placement. There are also Y-shaped hilar stents available (8, 10).

### ***2.2.2.1 Uncovered self-expandable metallic stents***

The biliary SEMS are made of metal alloys such as nitinol, stainless steel, Platinol™, or Elgiloy™ (5, 9). The metal mesh is either cut from a metal cylinder or braided from single or multiple metal wires (5). The open cell size of the metal mesh differs between stents, affecting the stent's features. From a technical point of view, the lower (<5%) shortening rate for uSEMS relative to that of cSEMS (20–40%) contributes to an easier deployment of the aforementioned (10).

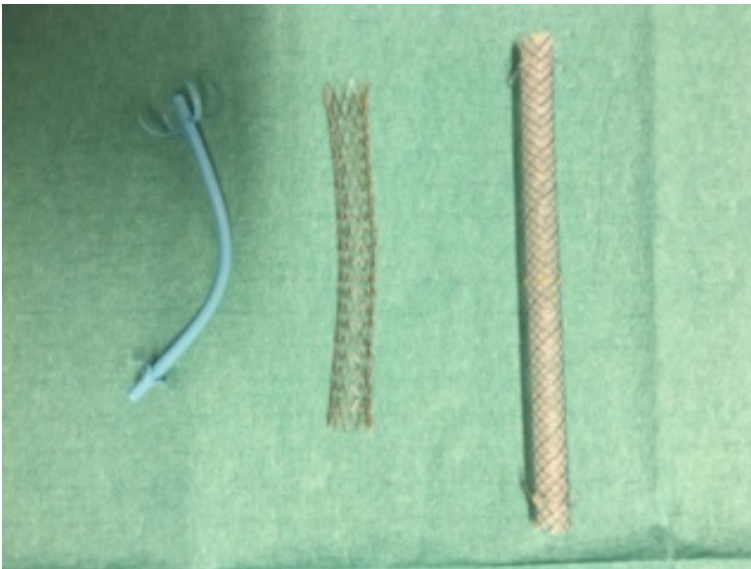
Occluded uncovered self-expandable metallic stents (uSEMS) can be mechanically cleansed, although with poor effect for restoring stent patency. Insertion of a second cSEMS into the occluded one is recommended to restore stent patency. In cases of a life expectancy shorter than 3 months, a NEPS can be chosen instead (6).

### 2.2.2.2 Partially and fully covered self-expandable metallic stents

To prevent tissue ingrowth, SEMS are covered, thus facilitating stent removal. Frequently used materials are polyurethane, silicone, and PTFE (i.e. Teflon™) (5). The cover may extend over the entire stent length (fcSEMS) or leave the outer ends of the stent uncovered (partially covered SEMS [pcSEMS]). The pcSEMS were originally designed for malignant strictures, but have been used in benign indications as well, especially in the early course of SEMS placement in BBS (11). Originally, it was thought that the bare ends would prevent migration, but for all cSEMS migration is a downside resulting from the covering and lack of ingrowth (12-15). The removal of pcSEMS can be impaired due to tissue ingrowth at the ends. On the other hand, there are reports of difficult removal of fcSEMS due to proximal migration and/or hyperplastic overgrowth at the ends of the stent (16). The reported migration rates for fcSEMS are up to 40% (14, 17-20).

Another drawback, connected to cSEMS is de novo strictures arising from a different area of the stent than the original stricture. An excessive radial force is assumed to induce local ischemia and subsequent stricture. If the stent diameter is oversized for the duct, the patient is prone to de novo strictures (15, 21).

When cSEMS were first introduced, a concern was occlusion of the cystic duct in patients with intact gallbladder, causing cholecystitis. An increased risk for pancreatitis caused by occlusion of the pancreatic duct in the papilla, was noted with use of cSEMS (22). Some studies indicate that high axial force of the stent, rather than the cSEMS itself, is associated with higher incidences of pancreatitis and cholecystitis (23).



**Figure 1.** Tannenbaum™ plastic stent, uncovered SEMS and fully covered SEMS with antimigratory flaps



### 2.2.3 BIODEGRADABLE STENTS

Kemppainen et al. described the first animal biodegradable stent (BDS) in 1993 (24). Although BDS have been used in humans as well, their use in the pancreaticobiliary tract and the gastrointestinal tract in general, is somewhat explorative (25, 26).

The goal and rationale for development of biliary BDS is the potential to achieve patency and a radial force similar to that of fcSEMS without the need for stent retrieval. Moreover, the NEPS- and cSEMS-related issues regarding stent migration and difficult removal could be disregarded (26).

The most commonly used BDS materials are polyglycolide (PGA), poly-caprolactone (PCL), polylactic acid (PLA), polydioxanone (PDX) and poly-lactide-co-glycolide with a magnesium alloy base (25). The degradation of the polymers is well known because of their previous use as suture materials. The slower (3–6 months) degradation and higher flexibility of PDX seems to be beneficial, as this may help in preserving the mechanical properties of the stent longer than with other polymers (27). The majority of pancreaticobiliary BDS reports are animal studies (28–32). In humans, the biliary BDS have been inserted using the PTC route, as no endoscopic insertion device was available (27, 33). In 2010, Hajer et al. reported the placement of an Ella™Dv stent using a mother endoscope to facilitate the insertion of the 15 Fr introduction sheath (31). Recently, Siiki et al. reported the first endoscopic insertion of a custom-made biliary PDX BDS in postoperative cystic duct leakage using a standard duodenoscope (34).

One challenge related to BDS is the lack of radiopacity in the materials (30). This can be overcome by mixing barium sulphate into the biodegradable stent material or by adding radiographic markers to the stent (25, 28, 30, 35). Another challenge is that the currently available Ella™Dv stent requires a 15 Fr sheath to be introduced (27). Therefore, the placement has been percutaneous, except for the previously mentioned report using a mother endoscope for the procedure (27, 31). Concerns regarding the impact of the stent material and degradation on the duct tissue have been raised. A porcine study on biliary stenting using a PDX stent showed transient, mild, or moderate hyperplasia of the ductal mucosa (31).

### 2.2.4 DRUG-ELUTING, DRUG-COATED, AND RADIOACTIVE STENTS

To overcome the problem of stent clogging or impaired stent patency, particularly in MBS, preliminary research has been conducted on drug-processed stents. Gemcitabine, sorafenib and paclitaxel have been investigated (8, 36, 37). Paclitaxel has a mitosis inhibiting effect, antiproliferative activity and antifibrotic effects, justifying its piloting use in BBS (38). Animal models have mainly been used, but human pilot studies have also been conducted. A prospective, human, piloting, randomized controlled trial (RCT) compared paclitaxel-eluting cSEMS with conventional cSEMS

regarding patency and survival and showed no statistically significant difference between the stents (39). A paclitaxel study on mice revealed growth inhibition of pancreatic cancer and cholangiocarcinoma (CCA) by suppressing angiogenesis (40). The *in vivo* study by Farnbacher et al. showed significantly reduced encrustation in heparin-coated NEPS compared with uncoated NEPS, albeit without any clinical impact (41). As sludge clogging the stents contains bacteria, microbial byproducts and crystals of fatty acid, the impact of antibiotics and/or ursodeoxycholic acid on stent patency has been evaluated, but has shown no significant effect (42).

With the purpose of impairing tumor growth and prolonging patency, a radioactive agent, iodine-125 seed, can be implanted in a stent, forming kind a of brachytherapy (43). Brachytherapy using holmium-166 has been shown to be safe in a canine model (8).

### 2.2.5 STENT FEATURES WITH FUNCTIONAL CONSEQUENCES

To overcome or compensate certain stent-related drawbacks and complications, several stent features have been developed. The above-mentioned drug-coating and drug-eluting can be considered as functional properties of a stent. Antimigratory stent elements used on (c)SEMS are anchoring pins protruding from part of the stent, flared ends, and anchoring flaps (43). These elements have been used alone and in combination, and furthermore, they can be located in different parts of the stent. There are also NEPS with anchoring flaps (5). Recently, Walter et al. reported a fairly high migration rate, 31%, when a nitinol fcSEMS with bilateral flare ends and irregular cellspaces was used (20). On the other hand, a study of otherwise similar fcSEMS, with or without flared ends, revealed a 40% migration rate with stent ends flared, compared with a migration rate of 100% when unflared stents were used (8). Mangiavillano et al. reported a migration rate as low as 3.3% using a new fcSEMS with proximal anchoring flaps and a double lasso system for retrieval, enabling intracholedochal deployment with no need for the stent to cross the papilla (44).

Weigt et al. very recently reported the use of a double-coned cSEMS mimicking the spindle-shape of the CBD, with the purpose of reducing the migration rate in 11 patients. The distal part of the stent was 12 mm, with a diameter diminishing towards the duodenal end. The stent was at its narrowest (6 mm in diameter) 15 mm from the duodenal end, whereafter the diameter increased again in a cone-like shape. The mechanical properties of the stent were measured and compared with those of a cylindrical shape from the same manufacturer, revealing that the radial forces at different points of the double-coned stent were less than half of those of the cylindrical stent. No migrations occurred, but three cases of stent occlusions were observed, two of them followed by cholangitis. Two recurrences (one CP and one AS stricture) were seen (45).

In 2009 Misra et al. reported that all patients in their study on biliary SEMS across the papilla had duodenobiliary reflux, constituting a risk for ascending cholangitis (46). This raised a theory on bile-food mix and biofilm induced stent clogging, and stents with antireflux valves were developed (43). Often the drawback cited for these stents was impaired drainage. However, some studies showed increased patency when antireflux stents were used (8).

Benign anastomotic strictures are usually short. The use of long cSEMS exposes the sound duct tissue to pressure injuries like necrosis and fibrosis (47). Short cSEMS, again, are prone to migrate outside the stricture site (43). To prevent migration, the short stents can be shaped to, for example, have a waist thinner than the ends (48). To ease removal, a snare or a lasso hanging in the duodenum, can be attached (11, 43, 48).

When it comes to the NEPS, the new stent designs seem to focus on more pliable materials with the intention of reducing migration rates, as the stent more easily could conform to the shape of the CBD (8).

## **2.3 IMPACT OF STENT POSITION IN RELATION TO THE PAPILLA**

In 1998, Pedersen et al. published an RCT on MBS patients with the idea that the placement of the stent (NEPS) above an intact sphincter of Oddi might prevent migration of bacteria and deposition of organic material into the stent (49). There was no significant difference in overall stent performance between supra- and transpapillary positioned stents, even though stents placed above the sphincter of Oddi migrated more frequently. On the other hand, two small sample size studies with 13 and 10 patients, respectively, reported no migrations when, custom-made fcSEMS of length 4 cm were placed intraductally (11, 48). Another study revealed significantly longer patency for suprapapillary NEPS, but the number of patients in this study was fairly low (50).

## **2.4 BENIGN BILIARY STRICTURES**

### **2.4.1 ETIOLOGY AND CLASSIFICATION**

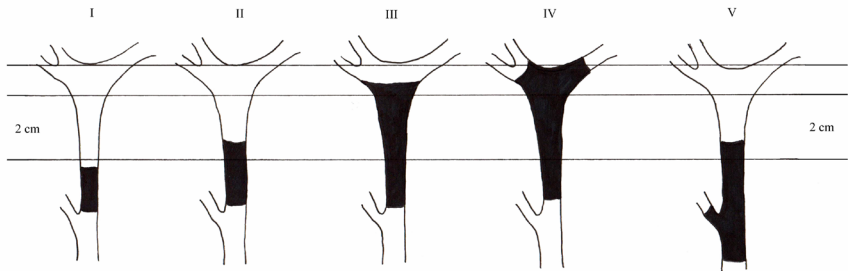
The most common type of BBS in Western countries is the postoperative stricture, which can occur secondary to intraoperative injury, most often after cholecystectomy. Anastomotic strictures also occur after orthotopic LT or following bile duct reconstructions (51). In CP, strictures develop in the intrapancreatic portion of the CBD. Infections including tuberculosis, histoplasmosis and the liver fluke *Clonorchis sinensis* (common in Asia) can cause BBS as well as HIV cholangiopathy. Other

causes include **PSC**, **sarcoidosis**, **recurrent cholangitis**, **abdominal trauma**, **ischemic injury**, **radiation- and chemotherapy**, **Mirizzi syndrome**, **vasculitis**, **papillary stenosis**, **choledochal cyst** and **dysfunction of the sphincter of Oddi**. The etiologies can be classified as **intrinsic or extrinsic**, **CP** constituting the most common cause of the latter (52).

**Table 1.** Etiology of benign biliary strictures.

<b>A. IATROGENIC</b> Postsurgical • Cholecystectomy • Liver transplantation • Biliary reconstruction  Radiation therapy Chemotherapy	<b>D. INFLAMMATORY</b> Chronic pancreatitis Primary sclerosing cholangitis Immunoglobulin IgG4 associated Cholangiopathy Sarcoidosis Vasculitis Mirizzi syndrome Choledocholithiasis
<b>B. ISCHEMIC</b>	<b>E. ANATOMICAL OR PHYSIOLOGICAL CAUSE</b> Choledochal cyst Dysfunction of sphincter of Oddi
<b>C. INFECTIOUS</b> Tuberculosis Histoplasmosis Recurrent cholangitis HIV cholangiopathy Parasites, e.g Clonorchis sincesencis	<b>F. OTHER</b> Abdominal trauma

In 1982 Bismuth classified postoperative biliary strictures based on their location, and other classifications for postoperative bile duct injuries have since been presented (53).



**Figure 2.** The Bismuth classification of benign biliary strictures based on stricture location. The location affects the repair technique.

## **2.4.2 CLINICAL PRESENTATION AND DIAGNOSIS**

Clinical presentation varies from slightly elevated blood liver function tests to complete cholestatic syndrome, including jaundice, pruritus, dark urine and whitish feces(54). Cholangitis can complicate the biliary obstruction, and CBD stones may occur above the stricture. Secondary biliary cirrhosis may develop as a long-term consequence in chronic cases (55).

The diagnosis is made based on elevated liver function tests and/or bilirubin levels and US scan of the upper abdomen, revealing dilated bile ducts. History of previous surgery on the biliary tree and its surroundings is crucial to evaluate the possibility of postoperative strictures (54, 56). Tumor markers can be helpful when a differential diagnosis for malignant cases is needed (57).

### ***2.4.2.1 Transabdominal ultrasound***

Ultrasound detects biliary obstruction along with the level of obstruction, with an accuracy exceeding 90%. The accuracy of detecting the underlying cause is much lower and varies from 30% to 70% (56).

### ***2.4.2.2 Magnetic resonance imaging***

Often MRCP is performed to evaluate the biliary tree and MRCP is the current non-invasive diagnostic method of choice for biliary strictures (58) . The sensitivity for the underlying cause of biliary obstruction is as high as 98%. The sensitivity in differentiating benign strictures from malignant strictures varies from 30% to 98% (56). Hepatocyte-specific MRI contrast material can help in distinguishing partial strictures from complete ones when using delayed phase imaging, as the contrast material is excreted into the biliary tree from the hepatocytes (58) .

### ***2.4.2.3 Multiphase contrast-enhanced computed tomography***

Computed tomography (CT) facilitates detection of the underlying cause of biliary obstruction, and reveals complications such as cholangitis and cholangitic abscess. CT helps to differentiate between benign and malignant strictures, although the distinguishing between CP-induced obstruction and MBS can be challenging. Malignant strictures are characterized by hyperenhancement and wall thickening. CT also reveals pathologic lymph nodes and metastases. Positron emission tomography (PET)-CT is helpful in unclear cases, offering a sensitivity and accuracy of 92% (56, 57) .

### **2.4.2.4 Endoscopic ultrasound**

Sometimes endoscopic ultrasound (EUS) can add information to the diagnosis (59) . It provides the possibility of accurate, guided fine needle aspiration. EUS is, however, highly user-dependent (56) .

### **2.4.2.5 Endoscopic cholangioscopy**

The currently widely used single-operator cholangioscopy is the SpyGlass™ Direct Visualization system (Boston Scientific Corp, MA, USA). During the procedure the SpyScope™ delivery catheter is introduced through the working channel of a therapeutic duodenoscope. The catheter has channels for the optic probe, irrigation, and instruments. The scope can be introduced into the bile duct for accurate visualization and allows the possibility for biopsies, making this a powerful diagnostic tool for biliary strictures (60) .

## **2.4.3 TREATMENT OPTIONS AND MANAGEMENT OF BENIGN BILIARY STRICTURES**

Historically, surgery and later PTC procedures have been the management of choice in BBS and anastomotic biliary complications (12, 61-63) . Complications and difficulties related to the poor condition of patients limit their use, and consequently, over the past 20 years, these procedures have been replaced by less invasive therapeutic ERCP(13). Complications occurring after ERCP include bleeding, perforation, and post-ERCP pancreatitis (PEP) and cholangitis, and there are consensus criteria for defining the severity of these complications (64) . Mild PEP is clinical pancreatitis with an amylase level higher than three times the upper limit at more than 24 hours from the procedure and a 2- to 3-day hospitalization. Moderate PEP requires a 4- to 10 day hospitalization. Severe PEP is defined by a need for hospitalization of more than 10 days or hemorrhagic PEP, presence of a pseudocyst or a flegmon, or need for percutaneous or surgical interventions. Initially, the therapeutic ERCP consisted of balloon dilation alone, with limited effect, with reported success rates being 27–41% (65). Later, placement of a single plastic stent, either with preceding dilation or not, comprised the procedure (66, 67). In 2001, Costamagna et al. reported successful use of multiple plastic stents in benign, postoperative CBD strictures, increasing the stent number in consecutive procedures (68) . Endoscopic treatment with NEPS is burdened by the need for repeat ERCs and stent exchange due to clogging every 3–4 months over a time period of 1–2 years (13, 69, 70). Definitive stenting with uSEMS, and later, when

available, with removable cSEMS were taken into use at the beginning of the 21st century (55, 71, 72)

Actually, it is not unequivocal whether stents should be placed instead of sole balloon dilation in all circumstances (38). If endoscopic access for some reason is hindered, PTBD can be performed (73). In some cases the PTC route can be used for rendezvous procedures (74).

Recently, Hu et al. performed intraductal radiofrequency ablation previously used in malignant cases for nine refractory BBS with a 56% success rate. The strictures were both intra- and extrahepatic and had various etiologies (75).

#### **2.4.4 ANASTOMOTIC BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION**

Post-LT biliary complications occur in 5–35% of cases (63). For deceased donor LTs the incidence is 5–15%, whereas for living donor LTs the figures range from 28% to 32% (76). Post-LT bile duct strictures can be classified as non-anastomotic (NAS) or anastomotic (AS), the latter accounting for about 40% of all post-LT biliary complications and up to 87% of post-LT BBS (62, 65, 76). The reported incidence for post-LT AS is 4–13% (65).

The incidence for post-LT anastomotic biliary leakage is 7% (77).

The most common bile duct reconstruction in LT is CC anastomosis (78, 79). Choledocho- or hepaticojejunostomy reconstruction is often used in LT indicated by PSC, biliary atresy and Caroli disease affecting the intrahepatic biliary tree (79).

##### ***2.4.4.1 Pathogenesis of and risk factors for post-LT anastomotic complications***

The AS is thought to result from suboptimal surgical technique causing ischemia and as a result of fibrotic healing (76, 80). Risk factors are previous or simultaneous bile leakage, small bile duct caliber, size mismatch between donor and recipient including female donor/male recipient pairs, inappropriate suture material, anastomotic tension, infection and pedantic hemostasis by electrocautery (62, 80). Albert et al. revealed a significant increase in AS in patients with viral or toxicity-induced hepatocellular carcinoma (HCC) in the recipient's cirrhotic liver (81).

##### ***2.4.4.2 Management of post-LT anastomotic biliary complications***

*Treatment with NEPS.* The technique with multiple plastic stenting was brought into use in post-LT AS as well, with success rates of up to 94% (63, 67, 68). There are also



dissenting opinions regarding such an aggressive approach in early postoperative anastomotic complications, reasoning that the acute, potentially reversible, local ischemia superimposed by edema will resolve if biliary ductal drainage is maintained by a single stent (67, 82). Progressive pneumatic dilation with double plastic stent placement has been considered the standard treatment for post-LT strictures (70).

A retrospective report of 47 patients' stricture recurrence after multiple plastic stenting identified late (> 6 weeks) occurrence of the stricture to be a significant risk factor for relapse, as was a high-grade (a luminal narrowing of at least 90%) stricture. There was also a tendency of recurrence in patients with hepatitis C virus (HCV), but competing risk analysis abated this finding (81).

*Treatment using cSEMS.* In 2006, Vandenbroucke reported the use of pcSEMS in post-LT strictures leaving the stent in place in the CBD (72). In cases of lost stent patency, surgery with a HJ was performed. In 2009 and 2010, two small sample size (n= 11 and 16) reports on deployment of fcSEMS in post-LT AS and/or leakages after failed endoscopic NEPS therapy were published with promising results (19, 83). Migration, without clinical consequences, was seen in 38% and 56% of patients. Recurrence or other treatment failure was seen in 6% and 30 % of cases. Tarantino et al., on the other hand, reported 71.8% success and 14.3% recurrence rates in post-LT AS and/or leakage when deploying fcSEMS for patients following failure of treatment with NEPS. In patients with fcSEMS as the first-line approach, the figures were 53.3% and 25.0%, respectively, and the authors concluded that fcSEMS placement is neither useful nor recommended as the first-line approach in post-LT AS. The migration rates for the first-line and second-line approach groups of 46.7% and 33.3%, respectively, were thought to explain the fairly high recurrence rates (70).

Phillips et al., again, in 2011, published a report on 17 patients with post-LT biliary leaks managed by intraductally placed, fully covered Viable™ stents with anchoring pins. All patients but one obtained long-term leak control, but six (35%) clinically significant strictures were recognized at stent removal, along with two (12%) clinically insignificant strictures and two biliary ulcerations confirmed on cholangioscopy. Some patients had strictures already when the fcSEMS was deployed, but the strictures were at a different site when the stent was removed, thus constituting de novo strictures. Furthermore, in two patients with hepatic artery thrombosis, the fcSEMS served as a bridge to surgery, controlling the leak to manage the infection sufficiently. The authors concluded that fcSEMS cannot be recommended for management of post-LT biliary leaks, although they recognized the possible influence of donor and hepatic artery factors, and more importantly, the choice of a stent with high radial force and anchoring pins, on the development of strictures and ulcers (47).

To date, Kaffes et al. have published the only prospective RCT comparing multiple plastic stenting with fcSEMS in post-LT AS. Stricture resolution was achieved in



80% and 100% of cases, respectively, with a nonsignificant difference. The number of ERCPs needed was significantly lower (2 vs 4.5,  $p = 0.0001$ ) in the fcSEMS group, and fcSEMS placement was also more cost-effective. Furthermore, there was a non-significant tendency towards fewer complications in the fcSEMS group ( $p = 0.051$ ). The median treatment time was 10.1 and 3.8 months, respectively and the corresponding recurrence rates were 37.5% and 33.3%. The number of patients in each group was 10 (48).

*Other treatment options.* Previously, coronary and crural arterial stenoses have been treated with intravascular paclitaxel-eluting, dilating balloons. A German group tried this procedure on 13 post-LT AS and showed a 92% (12/13) success rate. Two of the patients needed three interventions, one two interventions and the remaining nine one procedure only. The authors suggested further randomized, large-scale trials (38).

## **2.4.5 BILIARY STRICTURES IN CHRONIC PANCREATITIS**

Chronic pancreatitis induced CBD strictures are seen in 3–23% of cases (84). If the stricture is caused by inflammation or pseudocyst compression, it can be reversible, whereas a fibrotic stricture is irreversible (85). The ESGE guidelines recommend intervention for CBD strictures caused by CP in cases of symptoms, secondary biliary cirrhosis, presence of bile duct stones, progression of the stricture, or when unicteric cholestasis (i.e. serum alkaline phosphatase [AFOS] level greater than twice the upper limit) persists for longer than one month (86).

Even though surgery, consisting of Frey's procedure (coring out the diseased portion of the pancreas in combination with lateral pancreaticojejunostomy allowing biliary and pancreatic drainage), is considered the golden standard for treatment of CP-induced BBS, endoscopic treatment with multiple plastic stents is currently the first-line treatment choice as it is less prone to complications and also suits surgically unfit patients (59, 86, 87).

### ***2.4.5.1 Management of biliary strictures in chronic pancreatitis***

*Treatment with NEPS.* In the treatment of distal CBD stricture secondary to CP, the long-term clinical success rate has been reported to be 24% following single stent therapy versus 92% for multiple stent therapy (88). Other studies have revealed success rates ranging from 8% to 38% following single stent therapy and figures of 60–92% after multiple stent therapy (6, 88–90). Multiple stent therapy requires

several consecutive ERCP procedures, approximately trimonthly, in order to change clogged stents and increase the number of stents after balloon dilation (13, 68, 70).

*Treatment using cSEMS.* To overcome the inconvenience stemming from the need for stent exchange and amendment when plastic stents are used, cSEMS were brought into use also in CP-induced BBS (91, 92). Another argument for treatment with cSEMS is the lack of patient compliance with multiple procedures in this patient group, which often uses alcohol abundantly (57). The cSEMS durations in treatment of BBS in CP varies from 2 months to 1 year, with long-term success rates ranging from 46% to 93% (13, 52, 87, 91-93).

The main drawback with fcSEMS is their propensity to spontaneous migration (57, 92, 94).

Although, reports exist on definitive treatment with uSEMS (i.e. there is no intention to remove the stent) in CP patients, at present uSEMS are almost abandoned in benign states, as there are removable covered stents available (57, 71).

2.5 MALIGNANT BILARY STRICTURES

Malignant biliary strictures may result from direct tumor infiltration, extrinsic compression, adjacent inflammation, desmoplastic reaction (i.e. growth of connective tissue) or combinations of these (95). The tumor etiologies include pancreatic cancer, ampullary cancer, CCA, gallbladder cancer and metastatic disease expressed as an intrahepatic mass or lymphadenopathy (96-98). Fewer than 20% of these patients are candidates for curative resection, either being poor surgical candidates or having unresectable disease due to local spread or distant metastases (98). Biliary obstruction develops in 70–90% of unresectable cases, with endoscopic procedures as the treatment of choice for palliation (6, 95, 98). Preoperative biliary drainage for malignancy is debatable (1-3, 99-103).

Table 2. Etiology of malignant biliary strictures.

<b>PANCREATIC CANCER</b>	<b>CHOLANGIOCARCINOMA</b>
<b>AMPULLARY CANCER</b>	<b>METASTATIC DISEASE</b>
<b>CANCER OF THE GALLBLADDER</b>	<ul style="list-style-type: none"><li>• Intrahepatic mass</li><li>• Lymphadenopathy<ul style="list-style-type: none"><li>» portal</li><li>» distal biliary</li></ul></li></ul>

## 2.5.1 PALLIATIVE STENTING OR DRAINAGE

Endoscopic palliative drainage is effective in >80% of cases with a morbidity lower than in surgical interventions (6, 96). Large-bore SEMS have clearly longer patency than plastic stents (10). According to the ESGE guidelines, initial insertion of a NEPS is cost-effective in cases with a life expectancy shorter than 4 months; otherwise stenting with SEMS is more cost-effective (6). Another study drew the line at 6 months (104). The median patency for SEMS in MBS has been 9 months (98). A recent, randomized trial comparing the functional stent times for NEPS, uSEMS and pcSEMS showed a significantly longer functional time for SEMS (9–10 months vs. 5 months), without any significant difference in total cost per patient at one year (105). No difference in cost was present between uSEMS and pcSEMS. Furthermore, the total cost for patients with a short (less than 3 months) survival time not differ between NEPS and SEMS. Another prospective RCT from 2013 compared efficacy and complications for pcSEMS and NEPS in palliative stenting, revealing a significantly longer time to stent failure for pcSEMS (12 months) than for NEPS (5 months), and a fivefold cholangitis rate in the NEPS group (106).

If cSEMS are used, their tendency to migrate might outweigh the advantage of long stent patency and also spoil the argument for cost-effectiveness (23). Routine placement of NEPS in palliative conditions is not recommended, as their patency is limited to about 3 months (96, 98). If NEPS are used, approximately 50% of the patients require stent exchange due to clogging(96). A recent report by Nakai et al. recognized cSEMS with a low radial force, chemotherapy, and duodenal invasion as significant risk factors for cSEMS migration in distal MBS (23).

Besides longer patency due to their larger diameter, SEMS have the advantage of a relatively narrow, 8 Fr delivery system, making the passage across the stricture easier (96).

The downside of uSEMS, which were used from the beginning of the metal stent era, is eventual dysfunction due to tumor ingrowth and/or overgrowth (10, 98). To overcome this problem, cSEMS were developed (10, 23). Kitano et al. prospectively, in a RCT, compared partially covered and uncovered SEMS (n= 60+60) in the palliation of distal biliary obstruction due to unresectable pancreatic cancer. Both stents had a relatively low axial force and uncovered, flared ends to prevent migration. Both patient survival without stent dysfunction (median: 187 vs. 132 days;  $p = 0.043$ ) and stent patency (mean  $\pm$  SD:  $219.3 \pm 159.1$  vs.  $166.9 \pm 124.9$  days;  $p = 0.047$ ) were significantly longer in the pcSEMS than in the uSEMS group. Reintervention for stent dysfunction was performed on 23% of pcSEMS patients and 37% of uSEMS patients, with a non-significant difference ( $p = 0.08$ ). No migrations occurred in either group (107).

The use of cSEMS in MBS raised concerns regarding cholecystitis and pancreatitis, as it did in BBS. A meta-analysis from 2013 did not reveal any differences in pancreatitis or cholecystitis rates between uSEMS and cSEMS (108). The ESGE

guidelines recognized neoplastic involvement of the cystic duct and gallbladder stones as key risk factors for SEMS-related cholecystitis (5).

Meta-analyses comparing uSEMS with cSEMS regarding stent patency in patients with MBS, have revealed a longer patency for cSEMS, with others finding an unclear benefit of cSEMS, as their migration rate is higher and they do not appear to have longer patency (108-110). A recent Swedish RCT revealed no difference in stent patency (median 153 vs. 127 days) or survival (median 154 vs. 157 days) between patients stented with covered or uncovered SEMS, suggesting that other factors, including cost, availability, stent length and personal preference, play a more important role in stent choice (111).

Cholangiocarcinoma can be classified based on location as intrahepatic, perihilar, and extrahepatic (112). Bismuth proposed a CCA classification with further subclassification of hilar tumors with respect to their proximal extension (98). In cases of unresectable disease with jaundice, biliary drainage is the treatment of choice (112). In cases of extrahepatic lesions, the principles of extrahepatic malignant stenting are applicable (98, 112). Hilar stenting, on the other hand, requires consideration of whether to perform uni- or bilateral stenting, and whether to use NEPS or SEMS, among other considerations (8, 10, 112).

As drainage by ERCP has been shown to be both safer and more successful, PTBD has been recognized as a salvage method in cases of unsuccessful endoscopic therapy or in cases of substantial intrahepatic disease (96, 112, 113).

If the diagnosis is uncertain at the time of biliary drainage, according to the ESGE guidelines, a plastic stent is preferred to avoid long-term complications of SEMS in benign strictures (6).

### ***2.5.1.1 Malignant biliary strictures in altered anatomy***

All reports on percutaneously administered SEMS in altered anatomy comprise malignant strictures for which uncovered self-expandable metallic stents (uSEMS) were used (114, 115). In 2009, Koornstra et al. presented a case report where a uSEMS was inserted with the rendezvous-DBE technique into a malignant stricture of the HJ (115). Primarily, the PTC route could be used only for drainage since the correct route to reach the jejunum could not be found. A more recent case report by Pinho et al. describes SEMS placement in a malignant stricture through the papilla with the rendezvous technique using SBE (116).

## 2.5.2 DISEASE-MODIFYING TREATMENT

In unresectable CCA, ERC has been combined with photodynamic therapy (PDT) utilizing the cytotoxic effect of light and a photosensitizing chemical produced locally at the stricture site (96, 112). At the end of the procedure a stent is usually inserted. A longer SEMS patency has been demonstrated when the stent is inserted immediately after local PDT therapy (112). In 2005 Zoeph et al. published a RCT showing that PDT and stenting significantly improved survival (21 vs. 7 months) compared with stent therapy alone in patients with unresectable CCA(117). This survival benefit has later been demonstrated in several heterogeneous cohort studies (112).

Intraductal, ERCP-directed radiofrequency ablation (RFA) was developed as a tool for endoscopy to induce necrosis in MBS (112). Contrary to local PDT, intraductal RFA does not seem to prolong stent patency, but appears to be an independent predictor of survival (118). Local RFA has also been used for management of tumor ingrowth in biliary uSEMS (112).

Adverse issues when using PDT include photosensitivity, with the need to avoid sunlight for 4–6 weeks, and, depending on the photosensitizer used, the cost, which can be thirtyfold that of a RFA catheter (112). The advantage regarding PDT is that laser light can travel through bile, whereas RFA needs direct tissue contact (112).

## 2.5.3 PREOPERATIVE BILIARY DRAINAGE

Obstructive jaundice correlates with impairment of hepatic function, development of cholangitis and disturbances in coagulation (119). Surgery during obstructive jaundice was recognized to correlate with higher risks already by Whipple in 1935, with similar reports up to 50 years later (120, 121). Whipple actually conducted a two-stage operation with biliary bypass in the first phase, and the actual pancreaticoduodenectomy later, when the obstructive jaundice had resolved. Preoperative biliary drainage can also be achieved percutaneously and endoscopically, the latter comprising the most frequently used method at present (122). In recent years, there have been studies reporting no benefit of PBD over early surgery within two weeks, whereas other studies have shown some benefit for conducting PBD (1-3, 99-101, 123). The use of routine PBD is thus controversial. In 2010, van der Gaag et al. published a multicenter, randomized trial comparing PBD with surgery within a week alone for patients with cancer of the pancreatic head. The PBD patients received a NEPS 4–6 weeks prior to surgery, with PTC drainage as a rescue alternative in the 6% of patients with unsuccessful endoscopic stent placement. The rate for serious complications was 39% in the early surgery group and 74% in the PBD group ( $p < 0.001$ ; RR for the early surgery group 0.54). Both PBD and surgery-related complications were included in these figures. The overall complication rate for PBD was as high as 46%. The difference in surgery-related

complications was non-significant (37% in the early surgery and 47% in the PBD group,  $p=0.14$ ; RR for the early surgery group 0.79) (1).

Later, between 2011 and 2014, a new patient cohort, consisting of patients with PBD using fcSEMS, was added to these same early surgery and PBD-using NEPS cohorts, the two latter functioning as historical controls. The PBD-related complication rate for fcSEMS was 24%, giving a RR of 1.9 ( $p=0.011$ ). The stent-related complications (i.e occlusion and stent exchange) were 6%, compared with 31% for the NEPS group ( $p=0.003$ ). The rate for surgical complications did not differ between the groups. The PEP rate for the fcSEMS cohort was higher (18%,  $n=9/49$ ; one severe PEP) than in the NEPS group ( $p=0.038$ ) (124).

A Cochrane meta-analysis from 2012 revealed a significantly higher occurrence of serious morbidity in the PBD group than in the early surgery group (RR 1.66; 95% CI 1.28 to 2.16;  $p=0.0002$ ), but no significant difference in overall mortality. The conclusion of the meta-analysis was that current evidence could neither support nor disprove PBD for patients with obstructive jaundice (125).

While some studies have shown an increase in postoperative infection complications and higher overall complication rates after PBD, others have revealed no difference or evidence of the above (2, 3, 99, 126-129).

PBD is clearly indicated in the presence of cholangitis or significant hepatic dysfunction secondary to prolonged obstruction (100, 122). In biliary obstruction PBD is also considered if logistics delay surgery or in cases of neoadjuvant chemoradiotherapy (122).

Smith et al. revealed a more favorable early, but not overall, survival in pancreatic cancer patients without jaundice. Low albumin ( $p = 0.016$ ), elevated AFOS ( $p = 0.011$ ) and elevated CRP levels ( $P = 0.021$ ) were associated with poorer overall survival, and a bilirubin level  $> 35 \mu\text{mol/l}$  at the time of surgery was a significant adverse predictor of early survival. However, the majority of these patients had undergone PBD ( $n=130$ ): only 25 had not, and furthermore, only 11 of these were jaundiced (101).

Initially, SEMS was thought to be contraindicated in resectable pancreatic cancer, as it was assumed that the stent would impair the biliary anastomosis or provoke inflammatory and fibrotic reaction around the stenting area, hampering surgical dissection (122, 130, 131). Later observations disproved this assumption (130, 132, 133).

Decker et al. found that PBD patients stented with SEMS had a significantly lower stent dysfunction rate than NEPS-stented patients (0/11; 0% vs. 7/18; 39%;  $p=0.02$ ) (134). Previous, figures of 15% and 93%, respectively, have been published (132).

## **2.6 DEVICE-ASSISTED ENTEROSCOPY ERCP**

Surgically altered anatomy occurs after total or partial gastrectomy with either Billroth II or Roux-en-Y reconstruction, after pancreaticoduodenectomy, duodenal or choledochal injuries, LT with HJ and RYGB for morbid obesity. This alteration means traditional ERCP with a duodenoscope is difficult and most often impossible (135, 136).

The insufficient length of the duodenoscope is the obstacle for performing traditional ERCP in altered anatomy. In recent years, this obstacle has been overcome using device-assisted enteroscopy (DAE) using double-balloon (DBE), single-balloon (SBE), or spiral enteroscopy (SE) (136, 137). Even though these techniques enable the HJ or papilla to be reached, there are still several limitations compared with conventional ERCP; the enteroscopes are front viewing unlike the lateral viewing duodenoscopes, the enteroscope lacks an elevator forming a drawback in cases of difficult cannulation of the papilla and standard ERCP accessories can often not be used due the longer and narrow (2.8 mm) working channel. In recent years, short DBE and SBE have become available, enabling the use of those conventional ERCP accessories that can be used in a narrow working channel (138-141)

### **2.6.1 MANAGEMENT OF PATIENTS WITH ALTERED ANATOMY USING PTC**

Traditionally, in patients with altered anatomy, biliary problems have been managed using PTC (142, 143). However, there is often a need for repeated or new interventional procedures. In BBS, the reported success rate using the PTC technique is 67–90% (143, 144). Complication rates of 5–35% have been reported (144, 145). If bile duct dilation is minor or absent, PTC has a higher complication rate or may not be feasible at all (73). Okuno et al. presented a series of six patients with altered anatomy and bile duct stone removal using the rendezvous technique after forming a puncture route through the gallbladder. They reported no complications other than one case of mild post ERCP pancreatitis (PEP) (74).

### **2.6.2 SURGICALLY ASSISTED TECHNIQUES**

Baron et al. reported an option of using the DBE to insert a percutaneous endoscopic gastrostomy tube (PEG) into the resected stomach. Through this opening, a duodenoscope could be passed to perform ERCP in altered anatomy (4). Law et al. described a series of five RYGB patients who had percutaneous assisted transprosthetic endoscopic therapy, where the excluded stomach first was



accessed with balloon enteroscopy, a retrograde percutaneous gastrostomy was then performed and bridged with an esophageal SEMS to gain antegrade access with a standard duodenoscope (146). Schreiner et al. compared DAE ERCP with laparoscopy-assisted ERCP through the remnant stomach in RYGB patients. They concluded that laparoscopy-assisted method was superior in patients with a Roux-en-Y and bilioenteric limb exceeding a length of 150 cm (147).

### 2.6.3 MANAGEMENT OF PATIENTS WITH ALTERED ANATOMY USING SHORT ENTEROSCOPES

Short balloon enteroscopes have been developed to facilitate the use of standard-length ERCP accessories (140, 142). The 2.8 mm-working channel limits the use of some appliances, e.g. SEMS. In addition, there are cases where the short DBE is unable to reach the target site, whereas a long DBE may be more efficient. In a retrospective, single-center report, Itokawa et al. found a statistically significant difference in insertion success rate between standard long and short balloon-assisted enteroscopy (89% vs. 50%) in HJ patients with Roux-en-Y reconstruction (141). After the Whipple procedure, the corresponding figures were 94% and 92%, with no significant difference. Recently Sakakihara et al. reported retrospective results of short DBE therapy on strictures of the choledochojejunal anastomosis in 44 patients. Cannulation was successful in 36 cases. If the dilator balloon was fully inflated (5 atmospheres) within 60 seconds they received dilation therapy only (n=19), otherwise treatment consisted of dilation and stent therapy (n=17). The stents used were 5–7Fr plastic stents. Whether single or multiple stenting was used was not disclosed. The stents were changed every 3–6 months until the stricture had resolved, defined by contrast material running out freely within 30–60 seconds. These patients needed up to six stenting (and therefore DBE) episodes (mean 3.1). Four of the stented strictures did not resolve, still having stents at the end of the observation period. There was a recurrence rate of 26% in the dilation group and 15% in the dilation and stent group during follow-up. These were successfully retreated with the same protocol as initially and no further recurrences were found by the end of the observation period (139).

### 2.6.4 WORKING CHANNEL OF BALLOON ENTEROSCOPES

A thin working channel (2.8 mm) limits the use of accessories available. In 2014, Kawashima et al. reported a significant time difference in instrument insertion comparing a 168-cm-long DBE with a 2.8-mm working channel with a prototype



SBE (SIF-Y0004-V01; Olympus Medical Systems, Tokyo, Japan) of the same length with a 3.2-mm working channel, suggesting that channel width affects procedure time as well (148) . The same type of endoscope (model SIF-Y0004; Olympus Medical Systems, Tokyo, Japan), specially developed for ERCP use, was used in a report of Yamauchi et al. in 2014, considering ERCP in surgically altered anatomy with various indications in 22 patients. None of these patients had, however, BBS . Four patients had cSEMS inserted; the indications for these stents were not disclosed in the paper (149) .

### **3. AIMS OF THE STUDY**

Endoscopic stent therapy for extrahepatic biliary strictures was evaluated. Individual aims of the studies were as follows:

- I. To analyze the therapy outcome of biliary strictures or leaks occurring after LT when managed with removable partially or fully covered self-expandable metallic stents.
- II. To compare surgical outcomes in PD or TP patients with preoperative biliary drainage with either plastic or self-expandable metallic stents, with a supplementary analysis of operated patients without preoperative endoscopic stenting.
- III. To compare the feasibility and safety of removable fully covered metallic stents with multiple plastic stents in the therapy for CP-induced biliary strictures.
- IV. To describe the equipment and technique used in endoscopic benign bile duct stenting with cSEMS in patients with surgically altered anatomy, a technique that has not previously been possible/described.

## 4. MATERIALS AND METHODS

The study was carried out at Helsinki University Hospital, Department of Gastrointestinal Surgery (reorganized into Helsinki University Hospital Abdominal Center since January 2015). Studies I, II, and IV were retrospective in nature, requiring no approval by the ethics board. The prospective research of this thesis (III) was approved by the local ethics committee and registered at ClinicalTrials.gov with the identifier NCT01085747.

All patients in Studies I and IV were treated at the Unit of Therapeutic Endoscopy of Meilahti Hospital at Helsinki University Hospital, as were the majority of the patients in Studies II and III. However, 27 (14%) of 191 preoperatively, endoscopically stented patients in Study II were stented at other hospitals, as were 12 (20%) of 60 patients in the multicenter study (III).

All patients were consciously sedated for the ERCP procedures by an anesthesiologist.

The definitions and gradings of ERCP-related complications were based on consensus criteria (150) .

### 4.1 STUDY I

Between March 2008 and May 2010, 17 liver-transplanted patients with a CC-anastomosis and an anastomotic bile complication (16 strictures, 1 leak) received a cSEMS. Five patients had previously received a single, diagnostic NEPS. Data were retrospectively collected from patient charts and cholangiograms. The study is of a descriptive nature.

*ERCP technique and equipment used.* The papilla was cannulated using a sphincterotome with a guidewire. Patients with a native papilla had sphincterotomy. The anastomotic leak or stricture was identified and measured on fluoroscopy using a guidewire balloon and contrast media. All but one patient were stented with an Allium™ stent (Allium Medical Solutions Ltd, Caesarea Ind. Park, Caesarea, Israel) made of a super-elastic nitinol with a polymeric material cover. The anchored model of the stent was used in all cases but one. The stents expanded to a 10-mm diameter and were 6, 8, or 10 cm long. Three Allium™-stented patients initially received a 6- to 8-cm-long partly covered Wallstent™ (Boston Scientific Corp., Boston, MA, USA), as fully covered stents were not yet available at that time. Two patients were stented with a custom-made, fully covered Micro-Tech stent (Micro-Tech, Nanjing, China), one of whom initially had an Allium™ stent. These stents were 3 and 4 cm long and

chosen in order to obtain experience of short stents in the current indication. The stents, except for the Wallstents™, were placed entirely inside the CBD.

Biliary cSEMS had not previously been used in CC-AS at our unit and experience worldwide in their use was scarce. The optimal or even maximal indwelling time was not known. Therefore several patients, mainly at the beginning of the study, had a premeditated stent exchange 3–4 months from deployment.

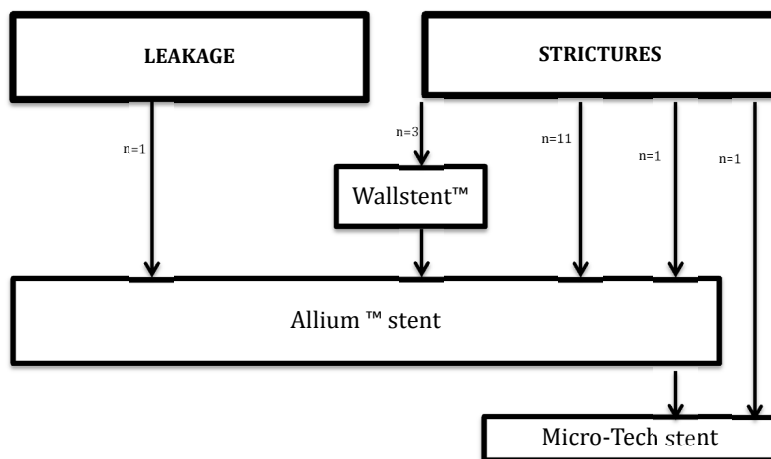
*Follow-up.* The patients were clinically evaluated at routine post-LT control visits or, if needed, at additional check-ups.

**Table 3.** Patient characteristics (I).

Number of patients	17
Gender: M/F (%)	7/10 (41/59)
Age (years) at first stent placement: median (range)	40 (18–61)
Received liver, n:	
- cadaveric reduced size	1
- cadaveric full size	16
Indication for LT, n (%):	
- acute or subacute liver failure	6 (35)
- alcohol cirrhosis	5 (29)
- Wilson's disease	2 (12)
- alcoholic steatohepatitis/autoimmune hepatitis	1 (6)
- PBC	1 (6)
- autoimmune hepatitis/PSC	1 (6)
- Budd-Chiari syndrome <sup>1</sup>	1 (6)
Indication for stent therapy, n:	
- anastomotic stricture	16
- anastomotic leak	1

M: male, F: female, LT: liver transplantation, PBC: primary biliary cirrhosis, PSC: primary sclerosing cholangitis

<sup>1</sup> The patient had a re-transplant due to chronic rejection.



**Figure 3.** Illustration of the stents used (I).

## 4.2 STUDY II

The surgical databases of Helsinki University Hospital searched for patients having had PD or TP during 2000–2009, yielded 366 patients. Of these 191 patients had endoscopic PBD and nine patients preoperative PTC. The endoscopically stented patients were divided into NEPS and SEMS groups and the unstented patients were grouped as patients with (UBO) or without (UNO) biliary obstruction. Patient characteristics and other variables were collected from patient charts and gathered in a Microsoft Windows Access™ database. The NEPS used were 10 Fr in diameter and 4–7 cm long. The metallic stents used were both covered (n=10) and uncovered (n=18) and 4–8 cm long, expanding to a diameter of 10 mm. The choice between covered and uncovered stents was based on the endoscopist's occasional preference.

Bacterial culture results on intraoperative bile duct juice samples were obtained for 156 cases; 141 were preoperatively stented patients, seven belonged to the UBO group and the remaining eight were unstented patients without biliary obstruction.

#### 4. MATERIALS AND METHODS

**Table 4.** Patient characteristics of stented cases (II).

Stented at ERCP	Total (n=191)			NEPS (n=163)			SEMS (n=28)		
	Median	Min	Max	Median	Min	Max	Median	Min	Max
Age (years)	64	35	82	64	36	82	64	52	79
Stricture length (cm)	2	0	6	2	0	6	2	0.5	4.5
CCI	0	0	6	0	0	6	0	0	5
ASA status (I-IV)	2	1	4	2	1	4	2.5	1	3
Pre-stent bilirubin (umol/l)	201	7	671	205	7	645	202	16	671
Preoperative bilirubin (umol/l)	21	3	460	21	3	460	31	5	414

CCI= Charlson comorbidity Index, ASA= American Society of Anesthesiologists' Physical Status Classification

**Table 5.** Patient characteristics of unstented cases (II).

PTC-drained and unstented	Total (n=175)			PTD (n=9)			UBO (n=9)			UNO (n=157)		
	Median	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max
Age (years)	61	25	83	66	57	74	65	31	75	60	29	78
CCI	0	0	9	2	0	5	0	0	0	0	0	9
ASA status (I-IV)	3	1	4	4	3	4	3	2	4	3	1	4
Preoperative bilirubin (μmol/l)	9	2	511	20	8	293	334	129	511	8	2	153

CCI= Charlson comorbidity Index, ASA= American Society of Anesthesiologists' Physical Status Classification

### 4.3 STUDY III

In a prospective, randomized, multicenter study, 60 consecutive patients with BBS caused by CP were stented by ERCP at Helsinki (n=48), Oulu (n=6) and Turku (n=6) University Hospitals. The patients were randomized using sealed envelopes between April 2008 and September 2012. All patients gave their informed consent.

**Table 6.** Patient characteristics (III).

	<b>Total (n=60)</b>	<b>NEPS (n=30)</b>	<b>fcSEMS (n=30)</b>	<b>p-value</b>
Male/female, n (male in %)	54/6 (90)	29/1 (97)	25/5 (83)	0.195
Age, years ; median (range)	53 (33–78)	49.5 (30–69)	54.5 (30–78)	0.160
Etiology of CP, n (%):				0.418
Alcohol	55 (92)	29 (97)	26 (87)	
Biliary	1 (2)	0 (0)	1 (3)	
Autoimmune	1 (2)	0 (0)	1 (3)	
Idiopathic	3 (5)	1 (3)	2 (7)	
Type of CP, n (%)				0.299
Chronic	50 (83)	27 (90)	23 (77)	
Acute on chronic	10 (17)	3 (10)	7 (23)	
Pancreatic calcifications, n	46	23	23	1.000
Gallbladder not removed, n (%)	48 (80)	23 (77)	25 (83)	1.000
Stricture length, cm; median (range)	3.0 (1.0–5.2)	2.5 (1.0–5.0)	3.0 (1.0–5.2)	0.436
Maximum diameter of the CBD above the stricture, mm; median (range)	13 (5–20)	12 (5–19)	13 (6–20)	0.632 0.604
Initial bilirubin; median(range) (4–20 µmol/l)	46 (5–275)	31 (7–244)	72 (5–275)	0.083
Initial AFOS; median (range) (35–105 U/l)	393 (50–1767)	320 (50–1040)	487 (86–1767)	0.111

NEPS, non-expandable plastic stent; fcSEMS, fully covered self-expandable stent; CP, chronic pancreatitis; CBD, common bile duct; AFOS, alkaline phosphatase

The initial ERCP was performed if biliary obstruction caused by CP was suspected based on elevated bilirubin and/or AFOS levels. All patients received a single NEPS after sphincterotomy. Clinical and laboratory findings were recorded at the time.

Randomization into NEPS or cSEMS groups occurred at the second ERCP 1–3 months later.

The cSEMS used were Hanarostent™, Wallflex™, and Wallstent™. The NEPS were progressively increased during the ERCPs, aiming at a total of six stents.

## 4.4 STUDY IV

Three patients with surgically altered anatomy were endoscopically stented with cSEMS. Endoscopic deployment of SEMS in patients with altered anatomy has not

previously been described in the literature. Therefore the partly novel equipment and management techniques are described in detail below.

**Patient 1** was a 73-year-old male with previous Billroth II-type gastric resection. In January 2014 the patient developed cholecystitis complicated by a subphrenic abscess, which was drained, and the patient received antibiotics. As a bilioenteric fistula was suspected, a DBE ERC was performed. Even though the papilla was reached, the CBD could not be cannulated. Fluoroscopy showed air in the biliary tree, strengthening the suspicion of a bilioenteric fistula. Thus, and also due to established cholecystitis, in May 2014, the patient had an open cholecystectomy, during which a T-tube was placed in the CBD. A distal stricture of the CBD was seen on cholangiography one week later and DBE ERC was re-attempted.

**Patient 2** was a 57-year-old female with Crohn's disease and PSC. She received a LT with a HJ reconstruction in 1998. During the summer of 2013 the patient suffered from recurrent cholangitis episodes, requiring treatment with antibiotics. In October 2013, a short stricture of the HJ and slightly dilated intrahepatic bile ducts in segments II and III of the liver were discovered on contrast-enhanced MRI. A prophylactic antibiotic was administered. As the changes persisted six months later and biopsy showed stage I fibrosis along with cholangitis raising a suspicion of PSC relapse, PTC was performed. The PTC drainage did not work sufficiently despite several drain changes, and thus, a rendezvous procedure using DBE was attempted.

**Patient 3** was a 72-year-old female with a previous pancreaticoduodenectomy in August 2013 due to T2N1 neuroendocrine tumor in the head of the pancreas. The patient suffered from relapsing cholangitis episodes, suspected to be caused by stricture of the HJ anastomosis.

##### 4.4.1 EQUIPMENT AND THE PROCEDURES IN DETAIL

A Fujifilm DBE (model EN-450T) with a 200-cm working length and a 2.8-mm working channel (Fujifilm Corp., Tokyo, Japan) was used during the procedures in Patient 1 and 2. In Patient 3, a Fujifilm DBE (model EN-580T) with a 200-cm working length and a 3.2-mm working channel (Fujifilm Corp.) was employed. A 145-cm-long and 13.2-mm-wide TS-13140 overtube with a transparent hood attached to the tip of the scope was employed in all three cases. During the procedure all patients were in prone position and under conscious sedation controlled by an anesthesiologist and a nurse. CO<sub>2</sub> insufflation was used in all procedures. The wires, catheters, and stents for the individual cases are presented separately hereafter.



**Case 1.** In June 2014, the DBE was intubated to the papillary area. Through the T-tube, a guidewire (HydroSteer™; St. Jude Medical, Minnetonka, MN, USA) was inserted into the duodenum. With a balloon catheter (triple-lumen extraction balloon; Endo-Flex GmbH, Voerde, Germany) on the guidewire, a Jagwire™ (Boston Scientific, Alajuela, Costa Rica) was inserted through the T-tube into the duodenum and afterwards out of the mouth using a snare through the enteroscope. Through the mouth and over the Jagwire™ running alongside the enteroscope, under fluoroscopic and endoscopic control, an fcSEMS (4 cm long, 10mm diameter; Niti-S biliary covered stent [Kaffes™; TaeWoong Medical Co., Ltd., Gyeonggi-do, South Korea]; 9 Fr, 180 cm introducer) was inserted into the CBD. The T-tube was removed.

**Case 2.** When the DBE was intubated, the endoscope started looping in the distal part of the afferent jejunal limb, preventing the scope from proceeding. Therefore, a guidewire (Radifocus™ non-vascular angled guidewire, 0.035 inch diameter, 450 cm long; Terumo Europe NV, Leuven, Belgium) was inserted through the PTC drain, to reach the enteroanastomosis. This was exchanged for a longer Jagwire™ (Boston Scientific).

With the help of a cut Ramp catheter (Haber Ramp™ catheter; Cook Medical, Limerick, Ireland) a second Jagwire™ was inserted and then both wires were pulled out through the mouth with the enteroscope. The enteroscope was drawn to the HJ area on one of the wires and with help of the other, a 3-cm-long fcSEMS (Niti-S biliary covered stent [Kaffes™]; 9 Fr, 180 cm introducer) was inserted and released under fluoro- and endoscopic control, verifying that the stent snare reached the bowel. To ensure later access with the DBE, a clamped PTC drain was left inside the stent. Even though an indwelling time of one year was planned, a check-up procedure was booked 3 months later.

**Case 3.** During the DBE the HJ was discovered to be very narrow, barely bypassed with a guidewire (FTE-Wildcat; 0.035 inch diameter, 650 cm long; pk endoskopie GmbH, Hannover, Germany). A needle knife (FTE-B2- papillotome; 250 cm long, 2.3/1.8mm diameter; pk endoskopie GmbH, Hannover, Germany) precut was performed and the anastomosis was dilated with a 10-mm dilation balloon (CRE wireguided dilatation catheter; 290 cm long; Boston Scientific, Natick, MA, USA). A custom-made 2-cm-long Hanaro fcSEMS, expanding to 10mm (Hanarostent™ fully covered biliary flap; 9 Fr, 230 cm long delivery device; M.I. Tech Co. Ltd., Gyeonggi-do) with antimigration flaps was deployed through the DBE working channel. To assess whether the stent had migrated or not, a plain abdominal X-ray was planned at 6 and 12 months from the procedure.



**Figure 4.** Fujifilm double balloon endoscope, model EN-580T, with a 200-cm working length and a 3.2-mm working channel (Fujifilm Corp.).

#### 4.5 CLASSIFICATIONS, GRADINGS AND SCORES

The ASA classification was used to characterize patients' physical health and the Charlson Comorbidity Index (CCI) with regard to certain pulmonary, cardiovascular, cancer and internal organ states was used to describe concomitant diseases (II). Postoperative pancreatic fistulas were graded according to the International Study Group of Pancreatic Fistula (ISGPF) classification into grades A, B, and C (II). Grade A fistulas are asymptomatic and transient chemical fistulas, not requiring further interventions. Grade B fistulas require minor therapeutic actions, e.g. endoscopic management, in symptomatic but otherwise stable patients. Patients with severe, clinically significant grade C fistulas appear unstable and ill, needing major therapeutic interventions.

To describe and quantify the bacterial cultures from the bile samples taken during the operation, a bacterial score was created (II). This score ignores the virulence of the microbes, considering only the number and amount of bacterial strains.

<b>I. Bacterial strains</b>		<b>Points</b>
no growth		0
one strain		1
two different strains		2
n	” ”	n
<b>II. Measure of microbes in 1st strain</b>		
”very scant”		0
+		1
++		2
+++		3
<b>N. Measure of microbes in n:th strain</b>		
”very scant”		0
+		1
++		2
+++		3

Bacterial score = I + II + . + ...+ N.

**Figure 5.** Illustration of how the bacterial score was calculated (II).

## 4.6 STATISTICAL ANALYSES

The calculations for statistical analyses in Studies II and III were performed using IBM SPSS™ (Statistical Package for the Social Sciences; v20, IBM Corp., Armonk, NY, USA), StatXact™ (v4.0.1, Cytel Software Corp., Cambridge, MA, USA) and in Study III alone Egret™ (v2.0.31, Cytel Software Corp.).

For the prospective study (III), sample size calculations were based on previous, non-randomized reports of BBS treatment in CP, with 90% treatment success using cSEMS compared with 60% success using NEPS. The parameters used for calculation were power= 0.8;  $\alpha = 0.05$ , giving a sample size of 60 patients (30+30).

Data are presented as median and range (I, II, III) or number of patients and percentage (I, II, III). The Kolmogorov-Smirnov test was used to test distribution normality for continuous data (II, III). Comparison of normally distributed continuous data was performed with Student's t-test and non-normally distributed continuous data with the Mann-Whitney U-test (II, III) or the Kruskal-Wallis test (II). To ascertain significant correlations between continuous data, the Spearman correlation coefficient was calculated (II). Hodges-Lehman median differences were calculated with 95% CI to assess differences in medians (III). Fischer's exact test

(II, III) or the Fisher-Freeman-Halton test (II) was used to determine differences in categorical variables, and the linear-association test was used to test trends in ordinal variables (II). For proportions, the exact Clopper-Pearsons confidence intervals were calculated (II, III). The Kaplan-Meier method was used for time-to-event analysis, and the differences between groups were assessed using the Log-Rank test (III). Two-sided p-values were used, and p-values  $<0.05$  were considered significant (II, III). For multiple testing, the p-values were corrected using the Bonferroni method (II).

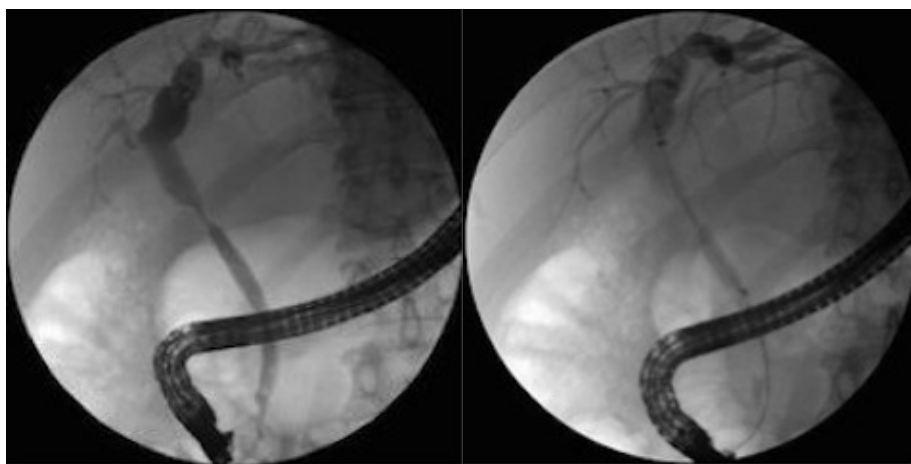
## 5. RESULTS

### 5.1 STUDY I

#### 5.1.1 ERCP, STENT THERAPY AND OUTCOME

Of the 17 patients with post-LT biliary strictures or leaks treated with cSEMS, two (12%) had a recurrence. The patients with recurrences were re-stented resulting in eventual stricture or leakage resolution in all patients. The total number of ERCPs performed was 58. The median number of procedures in each treatment entity (n=19) was three (2–6), with cSEMS deployment in 29. Balloon dilation to 6, 8, or 10 mm preceding stent placement was performed 19 times. There were seven procedures to check the stent and two planned ERCPs to ensure that the stricture had not recurred. Six patients (35%) had a stent exchange 3–4 months from placement, whereas eight (47%) were treated with only one stent. After stent therapy, decreased liver function tests were seen in all patients.

The one leakage patient received a second stent put partly inside the first one as the leakage continued. Even though the leakage resolved, the patient had repeated episodes of cholangitis, which were regarded as resulting from multiple ischemic hilar and intrahepatic strictures, leading to a retransplantation after several attempts of endoscopic therapy with NEPS.



**Figure 6.** ERCP pictures of an anastomotic stricture in a 56-year-old male, six weeks after liver transplantation, before and after stenting with an Allium™ stent (I).

### 5.1.2 STENTING TIME AND FOLLOW-UP

The median stenting time was 6.8 months (0.9–10.1). The longest indwelling time for a single stent was 9 months, and it was taken out without difficulty. During follow-up, which was 21.7 months (6.6–32.0) after stent removal, the liver function tests remained at the level achieved.

**Table 7.** Stent therapy in patients with anastomotic biliary complication after liver transplantation (I).

Patient no	Stent	ERCP no	Stenting time (mo) median 6.8	Recurrence (mo)	Complication	Follow-up (mo) median 21.7
1	2x Allium™	4	10.1		Anchor snap	32.0
2	Wallstent™ Allium™	4	9.9		1 <sup>st</sup> stent migrated	29.4
3 – 1 <sup>st</sup>	Allium™	2	0.9	1.4		
3 – 2 <sup>nd</sup>	Allium™	3	3.2			22.4
4	Wallstent™ 2x Allium™	6	9.7		1 <sup>st</sup> stent migrated below the stricture	26.0
5	Allium™	2	4.2			20.9
6	2x Allium™	3	9.7			28.5
7 – 1 <sup>st</sup>	2x Wallstent™	3	4.2	2.1	1 <sup>st</sup> stent migrated inside the CBD	
7 – 2 <sup>nd</sup>	2x Allium™	3	6.1		Cholangitis	28.7
8	Allium™	2	5			29.6
9	Allium™	3	6.7		Stent coming out in pieces + cholangitis	11.5
10	Allium™	2	9			21.7
11	2x Allium™	4	9			11.4
12	Allium™ Micro-Tech	3	8.2		1 <sup>st</sup> stent migrated below the stricture + anchor snap	25.9
13	2x Allium™	3	2.3		Cholangitis x2	8.7
14	Allium™	3	6.8			11.3
15	Allium™, unanchored	2	3.2		Mild pancreatitis + cholangitis	13.8
16	Micro-Tech	3	4.4			10.7
17	Allium™	3	6.8		Haematemesis	6.6

Mo = months, CBD = common bile duct

### 5.1.3 COMPLICATIONS AND DRAWBACKS

There were four stent migrations (24%), three of which occurred when a Wallstent™ was used, giving a 100% migration rate for Wallstent™. One of these was not detected on abdominal fluoroscopy during ERCP, indicating a complete migration. The fourth migrated stent, which had migrated just below the stricture, was an Allium™ stent, giving a 4% (n=1/23) migration rate for this stent type. It was replaced by a custom-made Micro-Tech stent. Two recurrences were seen, one following the treatment with a Wallstent™, the other after using an Allium™ stent.

There were complications connected to nine ERCP procedures (16 %). Cholangitis was seen five times (9%). The anchor of the Allium™ stent was broken off twice, without affecting the ability to remove the stent. One Allium™ stent was unravelled into metal filaments during removal, leaving the cover in the CBD. A FlowerBasket™ device (Olympus Medical Systems Tokyo, Japan) was used to remove the cover. This patient had postprocedural cholangitis and bacteremia, successfully treated with antibiotics. The indwelling time for this stent was six months. One patient (1.7%) developed PEP. This patient had concomitant cholangitis, and the PEP was deemed mild, although the hospital stay was markedly prolonged since the cholangitis was treated with intravenous antibiotics. One procedure was complicated with hematemesis two days after stent deployment. During a duodenoscopy a red spot found at the sphincterotomy was treated with a heat probe. No deaths occurred.

## 5.2 STUDY II

### 5.2.1 PRIMARY ENDPOINT: STENT FAILURE RATE

Initially, 168 (88%) of the 191 stented patients had a plastic stent. One was exchanged due to stent migration and twelve due to dysfunction. At the exchange, five patients received a SEMS. One cSEMS partially migrated towards the duodenum, resulting in dysfunction and stent exchange to a uSEMS. This resulted in 176 NEPS placements and 29 SEMS placements, giving a stent failure rate of 7.4% (95% CI: 4.0–12.3%) in the plastic group and 3.4% (95% CI: 0.1–17.7%) in the SEMS group, ( $p = 0.697$ , difference: -3.5%, 95% CI: -16.6–12.9%).

### 5.2.2 SECONDARY ENDPOINTS

The differences between the stent types regarding bilirubin levels, the bile juice bacterial level and postoperative complications were secondary endpoints of the study. The patients were arranged into groups according to their final preoperative stent type, resulting in 163 patients (85%) in the plastic group and 28 in the SEMS

group. The analyses were extended to comprise PD and TP patients having had preoperative PTD for biliary obstruction (n=9) and unstented patients with (UBO, n=9) or without (UNO, n=157) biliary obstruction.

### **5.2.2.1 Tumor size and neoadjuvant therapy**

When comparing NEPS and SEMS stented patients, no difference was present in tumor size ( $p=0.931$ ).

Twenty-five endoscopically stented patients (13%) had neoadjuvant therapy. The majority of them (n=22) had a NEPS. None of those receiving neoadjuvants needed stent exchange or additional ERCP procedures before surgery. The median time from stenting to surgery was 34 (3–102) days in the patients without neoadjuvant therapy and 110 (20–266) days in those receiving neoadjuvant therapy.

### **5.2.2.2 Bilirubin levels**

Neither bilirubin levels before stenting ( $p=0.732$ ) nor preoperative levels ( $p=0.157$ ) showed a difference between the stent groups. There were 171 patients with documented bilirubins both before stent placement and prior to surgery. Before stenting, 149 patients (126 with NEPS, 23 with SEMS) had a bilirubin level exceeding  $50 \mu\text{mol/l}$ . In the NEPS group 45% of patients reached a preoperative level of  $20 \mu\text{mol/l}$  or less. The corresponding figure in the SEMS group was 26% ( $p=0.110$ ). Eighty percent of patients in the NEPS group and 61% in the SEMS group had a preoperative level below  $50 \mu\text{mol/l}$  ( $p=0.058$ ).

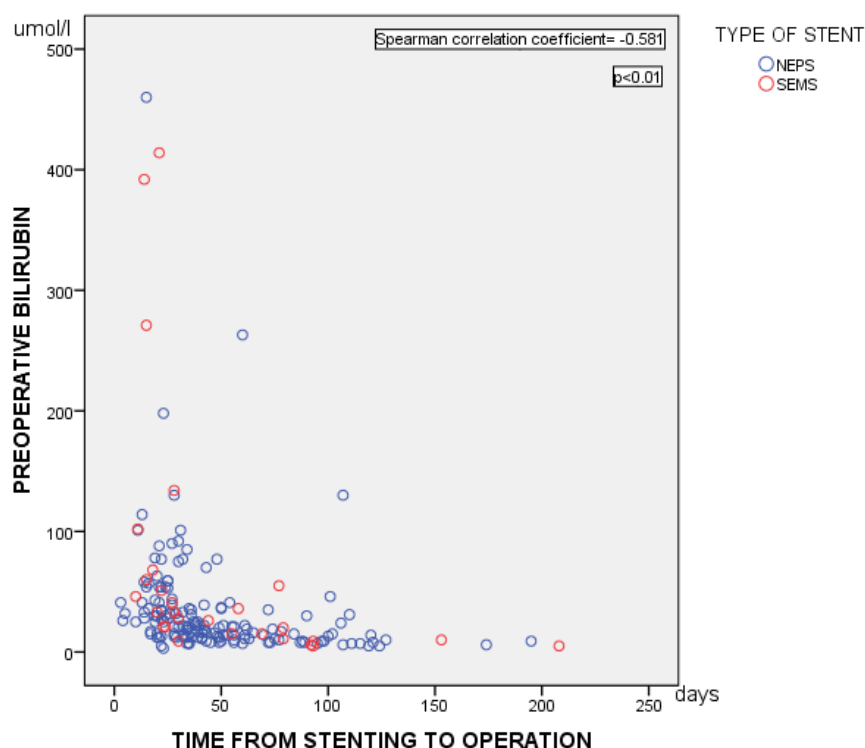
The preoperative bilirubin level was higher than that before ERCP in four NEPS patients and one SEMS patients. This could be described as a functional stent failure rate, which was 2.5% in the NEPS and 3.6% in the SEMS group, with no significant difference in the distribution between the groups ( $p=0.551$ ).

### **5.2.2.3 Bacterial scores of bile juice samples**

The intraoperatively obtained bile juice samples had a median bacterial score of 6 (0–23), with a median score of 6 (0–23) in the NEPS group and 6 (1–14) in the SEMS group. The mean difference in the score was 0.41 (95% CI -1.24–2.06). Of the stented patients only one (with a NEPS) had sterile bile, whereas all seven cases with documented bile samples among the unstented patients with biliary obstruction had sterile bile. The unstented patients without bile obstruction had sterile bile in 73%



of cases; the corresponding figure for PTD patients was 11%. When the proportion of sterile bile juices in unstented patients with biliary obstruction (100%; n= 7/7) was compared with that in stented patients (1%; n=1/155), a statistically significant difference emerged ( $p<0.001$ ). However, the groups were of very different sizes.



**Figure 7.** Graphic presentation of the correlation between the bilirubin level and time from stent placement to operation. The bilirubin level decreases as the time from stent placement increases.

#### 5.2.2.4 Infection complications

Infection complications arose in 28 endoscopically stented patients (15%). The complications were wound infections, including two at the origin of the vein graft (n=9), urinary tract infection (n=8), bacteremia (n=5), pneumonia (n=4), clostridium colitis (n=2), and intra-abdominal abscess (n=1). When the NEPS and SEMS groups were compared, no significant difference emerged ( $p=0.057$ ), as was the case when endoscopically stented and unstented patients with biliary obstruction were compared ( $p=0.365$ ).

### 5.2.2.5 Postoperative pancreatic fistulas

There were 183 PD patients with an endoscopically deployed stent. Twenty-six (14%) of these patients had a postoperative pancreatic fistula. No significant difference was seen in the distribution of fistulas between the NEPS and SEMS groups ( $p=0.072$ ). Even though SEMS patients had no Grade A fistulas and there were 18 (12%) in the NEPS group, the difference between the groups was not significant ( $p=0.238$ ). Nor was there a significant difference in the occurrence of fistulas when the stented patients were compared with the UBO group ( $p=1.000$ ). In the endoscopically stented patients, no difference was observed in the distribution of the bacterial score regarding the different categories of fistulas ( $p=0.596$ ). Nor was there a difference between the NEPS and SEMS groups when patients having a postoperative infection complication and/or a fistula were compared. There were 49 such patients, 42 (26%) in the NEPS and seven (25%) in the SEMS group ( $p=1.000$ ).

**Table 8.** Results for individual groups (II).

	NEPS (n= 163)	SEMS (n=28)	PTD (n=9)	UBO (n=9)	UNO (n=157)
Tumor size, median (range), mm	30 (5–150)	30 (7–150)	30 (23–35)	34 (13–70)	32 (9–140)
<b>Malignant tumors</b>	<b>n=110</b>	<b>n=22</b>	<b>n=7</b>	<b>n=8</b>	<b>n=38</b>
Stage, n (%)					
Stage I	22 (20)	1 (5)	1 (14)	1 (13)	12 (32)
Stage II	85 (77)	21 (95)	6 (86)	7 (87)	22 (58)
Stage III-IV	3 (3)	0 (0)	0 (0)	0 (0)	4 (10)
Neoadjuvant therapy, n (%)	22 (20)	3 (14)	1 (11)	3 (33)	1 (3)
Bacterial score, median (range)	6 (0–23)	6 (1–14)	6 (0–16)	0 (0–0)	0 (0–19)
Postoperative infection complications, n (%)	23 (14)	5 (18)	1 (11)	0 (0)	10 (6)
Fistulas, n (%)					
Grade A	18 (12)	0 (0)	1 (11)	1 (11)	47 (31)
Grade B	1 (1)	1 (4)	0 (0)	0 (0)	5 (3)
Grade C	5 (3)	1 (4)	0 (0)	0 (0)	1 (1)
Reoperations, n (%)	6 (4)	3 (11)	0 (0)	0 (0)	13 (8)

NEPS= patients with non-expandable plastic stent; patients with SEMS= patients with self-expandable plastic stent; PTD = patients with percutaneous transhepatic biliary drainage; UBO = unstented patients with biliary obstruction; UNO = unstented patients with no biliary obstruction

#### **5.2.2.6 Reoperations**

There was no difference between the NEPS and SEMS groups regarding the number of reoperations with indications other than Grade C fistulas ( $p=0.129$ ). The indications were leakage of the HJ ( $n = 3$ ), bleeding ( $n = 2$ ), mechanic stomach retention ( $n = 1$ ), suspicion of necrotizing fascitis ( $n = 1$ ), peritonitis caused by slip of the drain into the abdominal cavity ( $n = 1$ ), and thoracotomy due to massive bleeding after drainage of pleural fluid ( $n = 1$ ). Of the patients with a HJ leak, two were stented with a NEPS and one with a cSEMS. When endoscopically stented ( $n=9/191$ , 5%) and unstented ( $n=13/166$ , 8%) patients were compared for reoperations, no significant difference emerged ( $p=1.000$ ).

#### **5.2.2.7 Postoperative hospital stay and mortality**

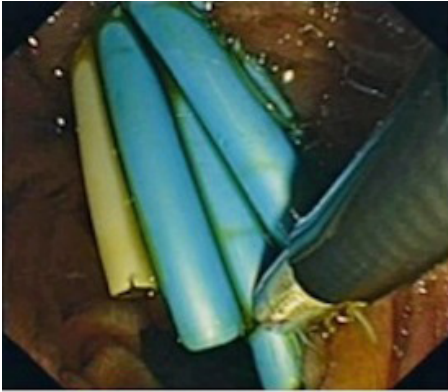
The median postoperative hospital stay was 11 (6–112) days in the NEPS and 12 (8–50) days in the SEMS group; thus no significant difference was present between the groups ( $p=0.750$ ). Both the unstented and stented patients had a 30-day postoperative mortality rate of 0%.

#### **5.2.2.8 ERCP-related complications**

The number of complications related to ERCP and biliary stenting was nine (4.7%). Two patients (1.0%) had post-ERCP bleeding. These were managed conservatively, even though the other patient had a duodenoscopy when the bleeding had already stopped. Seven cases of mild PEP (3.4%) were seen. There were no cases of severe PEP, perforations or procedure-related cholangitis.

### **5.3 STUDY III**

Of the randomized patients, two dropped out before the stents were removed. This resulted in a final sample size of 30 patients in the NEPS group and 28 patients in the SEMS group when the follow-up started. One non-compliant patient did not show up for the third ERCP, and thus, he ended up with only three NEPS. The remaining patients received four ( $n=1$ ), five ( $n=5$ ), and six ( $n=23$ ) stents. When comparing the total ERCP durations between the groups, the durations in the cSEMS groups were significantly shorter ( $p=0.008$ ).



**Figure 8.** Multiple plastic stents across the papilla.

### 5.3.1 STENT REMOVAL

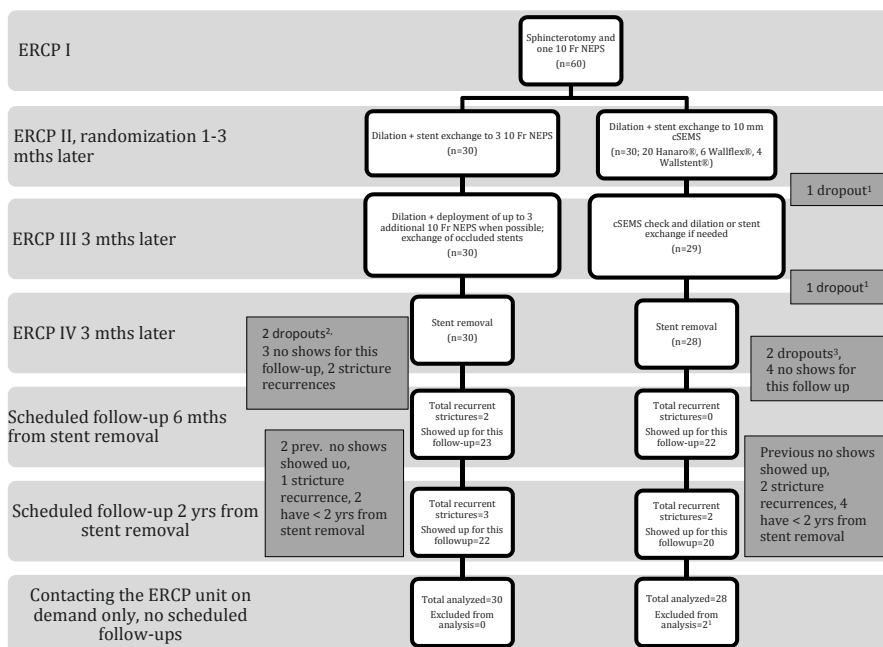
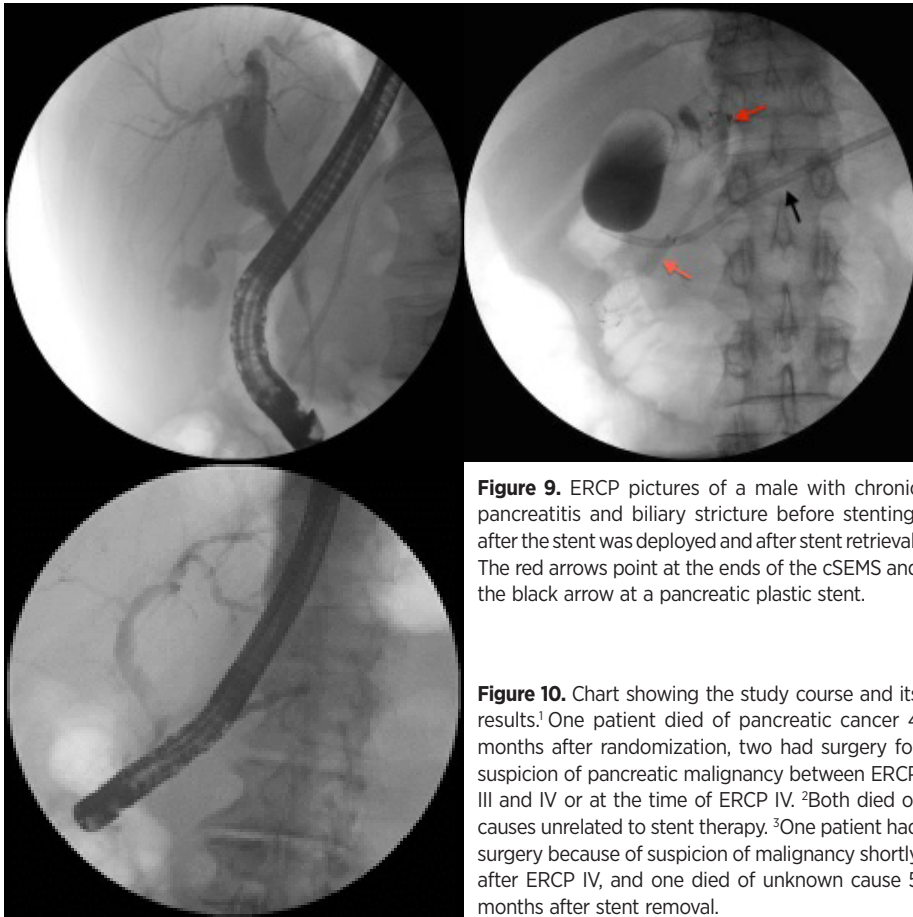
There were difficulties in removing four cSEMS in the early stages of the study. Two stents were discovered to be broken before they were removed. One of them was completely removed, the other only partially. The remnant remains in the patients CBD and has not caused problems during follow-up. One stent broke into two parts when removed. The other part was removed during another ERCP procedure with cholangitis as a consequence. When first attempted, a Wallstent™ could not be removed, needing successive ERCPs with placement of another cSEMS in the original one, until both stents eventually were removed.

### 5.3.2 FOLLOW-UP AND RECURRENCES

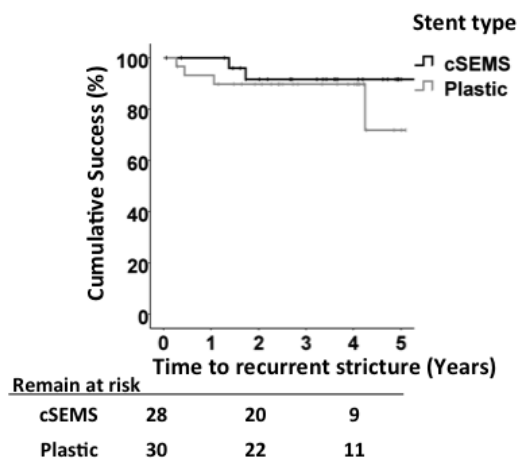
The median follow-up (April 2014), including the patients with recurrence, was 37 (3–61) months in the NEPS group, 41 (1–66) months in the cSEMS group, and 40 (1–66) months in all patients ( $p=0.832$ ).

At the initial and last ERCP, the strictures and CBD diameters above the strictures were measured. The bilirubin and AFOS levels were measured before stenting and at the follow-ups at 6 and 24 months after stent removal. Two years from stent removal 88% ( $n=36/41$ ) of the patients had a bilirubin level of 20  $\mu\text{mol/l}$  or less and 98% ( $n=40/41$ ) a level below 25  $\mu\text{mol/l}$ . There were no signs of CBD obstruction on US in the patients with values exceeding the normal limits. Findings indicating liver cirrhosis were seen at US of the patient with the highest bilirubin level (59  $\mu\text{mol/l}$ ).

There were five recurrences during the 2-year follow-up. Three of these were in the NEPS group and two in the cSEMS group. The success rates for the groups were 88% ( $n=22/25$ ; 95%CI 69–97%) and 91% ( $n=20/22$ ; 95%CI 71–99%), respectively



( $P=1.000$ ), with an overall success rate of 89% (42/47; 95%CI 77–96%). The patients were advised to contact the hospital in cases of symptoms or adverse events after the 2-year follow-up as well, resulting in further time-to-event data. Regarding this analysis, the success rates for were 90% (95%CI 72–97%) and 92% (95%CI 70–98%), respectively ( $p=0.405$ ). Additionally, one patient in the NEPS group had a late stricture 50 months after the stent was removed, diminishing the success rate for plastic stents to 72% (95%CI 27–92%).



**Figure 11.** Time-to-event analysis of recurrences of CP-induced biliary strictures managed by stents. The figure shows time passed from stent removal to observation of recurrent stricture (each step indicates one patient with stricture recurrence) in patients treated with multiple plastic stents or a single covered self-expandable metallic stent (cSEMS) for 6 months (III).

### 5.3.3 COMPLICATIONS AND ADVERSE EVENTS

Adverse events were found in seven patients (23%) in the NEPS group and eight patients (29%) in the cSEMS group ( $p=0.767$ ). Two patients (7%) in the NEPS group and four (14%) in the cSEMS group had cholangitis ( $p=0.415$ ). When the study started, 23 patients in the NEPS and 25 in the cSEMS group had an intact gallbladder. One patient from each group developed acute cholecystitis during stent therapy. The groups had three (10%) and two (7%) occasions of stent migration, respectively ( $p=1.000$ ). The plastic stents migrated proximally twice, and once into the duodenum. The cSEMS migrations (one proximal and one distal), observed at the third ERCP 3 months after stent deployment, were re-stented.

In the NEPS group two patients had pseudocyst infection and one patient's pancreatic stent had migrated and perforated the transverse colon through the duodenum during the follow-up, forming additional adverse events. Other adverse

events in the cSEMS group were one pseudocyst bleeding and one duodenal obstruction. These were thought to be unrelated to biliary stent therapy.

There was one case of mild PEP. As the total number of ERCPs was over 200, the PEP rate was 0.5%.

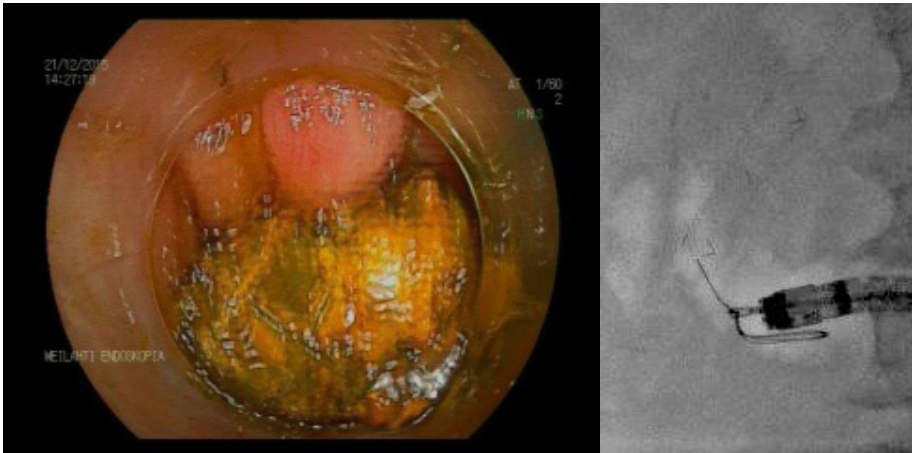
## 5.4 STUDY IV

**Case 1.** The fcSEMS was successfully deployed. A DBE ERC for stent removal was set up 6 months later. Before the scheduled procedure, the patient presented with a subcutaneous abscess at the operation wound scar in October 2014. On CT scan it communicated with a deeper 6 x 2 x 1.5 cm abscess located between the diaphragm and left liver lobe. The fcSEMS was in place and open. The abscess was successfully drained. One month later, the abscess had recurred. There was no communication with the biliary tree on CT fistulography, but the bile ducts in the left lobe were dilated. The liver function test and bilirubin levels were low.

The liver surgeons were consulted because of the persistent abscess. At the time the CT scan revealed a portal thrombosis. The abscess seemed to resolve conservatively when treated with antibiotics. As pus discharge through a skin opening persisted and the patient had recurrent episodes of fever, sanitizing surgery was scheduled. A laparotomy was performed in April 2015, revealing that the fistula was connected to the hilar site. Affected were liver segments II and III, revealed by peroperative cholangiography, and these segments were resected along with a part of segment IV.

The patient recovered well from surgery. The CT scan in August 2015 revealed no signs of leakage or abscess residue. The stent and biliary tree contained air as a sign of stent patency. Clinical follow up in October 2015 revealed normal laboratory findings and clinical recovery.

In December 2015, the patient presented with upper abdominal pain, fever, and elevated AFOS and bilirubin levels. The CT scan revealed no air in the biliary tree as a sign of stent occlusion and, surprisingly, a pancreatic tumor with multiple lung metastases. A DBE ERC was performed, showing an occluded cSEMS, which was removed. The patient was referred for palliative oncologic treatments.



**Figure 12.** Endoscopic view of the incrusted cSEMS in Case 1 before removal. The removal of the stent by pulling a snare is seen on fluoroscopy.

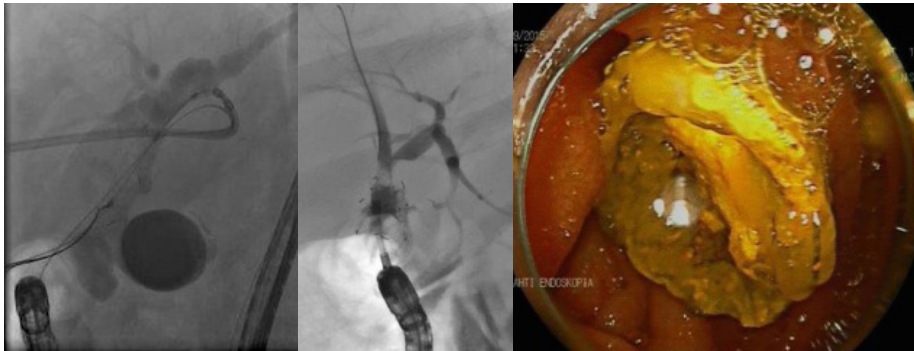
**Case 2.** In the DBE ERC three months after deployment, migration of the previously successfully deployed fcSEMS was observed. The stent had migrated above the anastomosis into a bile duct. A 13-mm balloon (triple-lumen extraction balloon, 250cm long; Endo-Flex GmbH) was passed through the anastomosis without difficulty and the stent was removed. The stent was not replaced as the HJ was well open, and the PTC drain was removed.

One year later, the patient had a scheduled post-LT follow-up. She had had episodes of fever with upper abdominal pain monthly, which presumably were episodes of cholangitis. A MRCP was performed, showing an obvious stricture in a right central biliary branch with concomitant intrahepatic bile duct dilation. Similar minor and more diffuse findings were made in the left liver lobe. There was also contrast enhancement of the bile duct walls as a sign of cholangitis. As the patient's symptoms were transient and mild, the liver surgeons decided to treat the episodes with antibiotics for a short time. If the situation becomes worse DBE ERC will be considered.

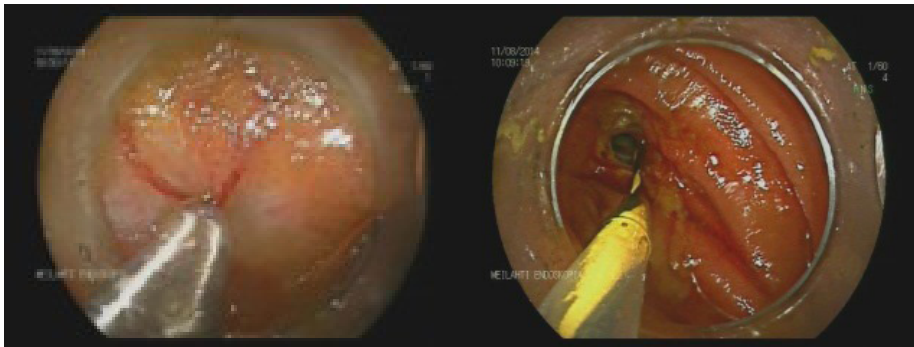
**Case 3.** The fcSEMS was successfully deployed through the DBE channel. A follow-up including plain abdominal X-ray was set up 12 months later to determine whether or not the stent had migrated. If migration had not occurred at that time, removal using DBE ERC would be scheduled.

As the stent was in place on the X-ray, DBE ERC was performed and the stent was removed without difficulty.

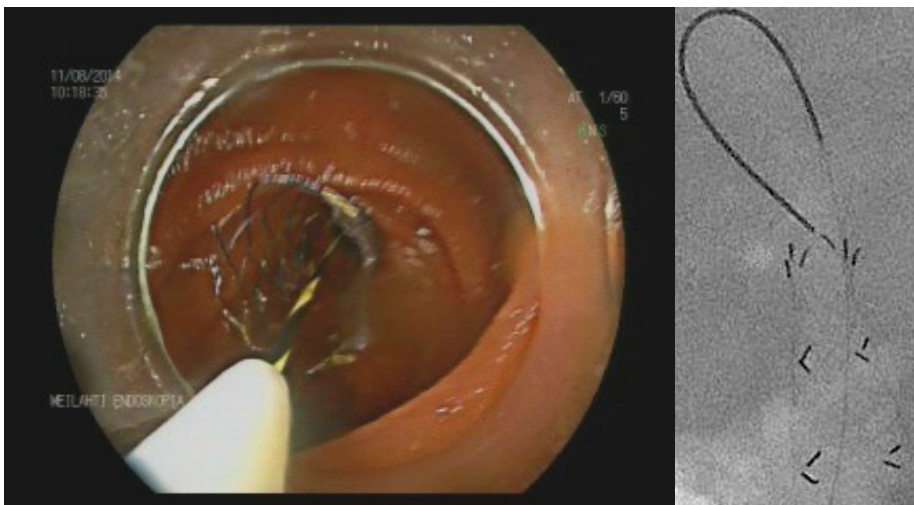




**Figure 13.** Deployment of the cSEMS in Case 2, and fluoro- and endoscopic view before stent removal.



**Figure 14.** Endoscopic view of the very narrow HJ in Case 3 before and after precut and dilation.



**Figure 15.** Endoscopic and fluoroscopic view of the deployed cSEMS in Case 3.

## 6. DISCUSSION

Endoscopic management of extrahepatic biliary strictures comprises numerous therapy approaches. Aspects to be considered before therapeutic ERCP include benign versus malignant stricture, length and location of the stricture, whether the stricture tissue is smooth or firm, and etiology of the stricture, among others. Furthermore, the management of malignant strictures can be palliative, preoperative or either of these in borderline resectable pancreatic cancer, the approach being determined after chemotherapy. Not only the properties of the stricture warrant consideration, but whether or not to stent must be decided. If stenting is needed, a choice between countless different stents with various properties must be made.

### 6.1 STENT THERAPY IN ANASTOMOTIC BILIARY STRICTURES AND LEAKS AFTER LT (I)

The first reports of using pcSEMS in post-LT anastomotic strictures were published in 2006 (72). The stents were left in the CBD without intention of retrieval, with surgery as a rescue procedure in case of stent dysfunction. Kahaleh et al. published a preliminary report on temporary placement of cSEMS in postoperative biliary leaks in 2007, and later, in 2008, a piloting study of cSEMS in various BBS including 16 post-LT strictures, with promising results (18, 151). Simultaneously, LT patients' ERCPs were reorganized and centralized to our unit at Helsinki University Hospital and (f)cSEMS for post-LT anastomotic complications was brought into use.

At this point, the use of cSEMS in benign indications was experimental both generally and at our institution, with no detailed design for this kind of stent therapy. For this indication, we mainly used a fully covered Allium™ stent, but in the early course of the study, partially covered Wallstents™ were used if the Allium™ was not available. The outcomes therefore cannot be directly compared. Moreover, two custom-made stents were used to acquire experience with short stents. As the Allium™ stent, according to our earlier experience, was prone to migrate in transpapillary usage, we decided to proceed with intracholedochal deployment of the Allium™ and the custom-made Micro-Tech stents. Indeed, only one Allium™ stent (4%), coincidentally discovered at a scheduled ERCP, migrated right below the stricture.

One unclear issue was the stenting time. It was unknown for how long a stent could be in place and still be removed. The optimal stenting time for stricture resolution was also not known. Therefore, the majority of our patients had routine stent exchange 3–4 months after stent placement. As transplant surgery in Finland

is centralized to Helsinki University Hospital, some patients travelled a considerable distance. It was thus preferable to have the ERCP procedures for these patients at the time of otherwise scheduled appointments, even though the timing for the procedure was not in accordance with the endoscopist's recommendation. This explains the various stenting times in our study. This practice also gave us valuable information on stent retrievability after an indwelling time longer than 4 months. The longest indwelling time for an individual stent, removed without difficulty, was 9 months. On the other hand, there was unravelling of an Allium™ stent after 6 months in situ, which indicates that factors other than indwelling time also have an impact on removability.

In 2010, Chaput et al. presented a prospective uncontrolled study, where post-LT strictures were stented with a pcSEMS for two months with a nearly 50% recurrence rate, indicating that this stenting time was a too short (152). In our material we had two recurrences, one after a stenting time of 4.2 months with two consecutive Wallstents™ and the other after only 0.9 months of stenting (stent removed due to clinical misjudgement) with an Allium™ stent. On the other hand, we had five patients with stenting times from 2.3 to 4.4 months without recurrences. In a RCT comparing fcSEMS with multiple NEPS, Kaffes et al. had a median stenting time of 3.8 (2.5–5.5) months and a 33% recurrence rate(48). Interestingly, none of these studies analyzed the recurrences with respect to the time passed from transplantation to stricture. Rajab et al. recently described a more conservative approach to postoperative biliary strictures, placing a single 10 Fr stent with or without preceding balloon dilation, showing an overall stricture resolution of 72% and in post-LT patients 78% (82). The median time for stricture formation was 0.7 months with an interquartile range (IQR) of 0.3–1.3 months in the successful group, compared with 1.9 (IQR 0.9–2.1) months in patients failing endoscopic treatment ( $p=0.07$ ). If spontaneous resolution of early AS is true, these could be managed by one NEPS maintaining the biliary flow, instead of subjecting the CBD to pressure from cSEMS or multiple plastic stenting with, at least, a theoretical risk for de novo strictures in this delicate patient group.

Overall, the results for cSEMS therapy in this study were satisfactory, as all patients eventually reached stricture resolution. On the other hand, as the study lacks a control group, it is unknown whether the same number of ERCP procedures for each patient with balloon dilation alone would have produced similar results. The need for re-transplantation in the sole leakage patient with eventual multiple hilar and intrahepatic strictures was probably not preventable, although a theoretical pressure-induced ischemia caused by the cSEMS cannot be ruled out.

Previously, multiple progressive plastic stenting has efficiently been used for management of post-LT AS with resolution rates as high as 94%, clearly competing with the results of this study and consistent also with earlier success rates for cSEMS (19, 47, 63, 67, 70). However, this kind of management lasts for one year, is laborious

considering the need for trimonthly ERCPs, adds to patient discomfort and is less cost-effective than management using cSEMS(48).

## 6.2 STENT THERAPY IN BILIARY STRICTURES CAUSED BY CHRONIC PANCREATITIS (III)

The therapy outcome for BBS caused by CP is poorer than for other etiologies, probably due to its fibrotic and frequently occurring calcifying nature, and therefore, surgery is a favored treatment option (51, 71, 84, 86) . At present, the recommended first-line treatment is temporary placement of multiple, plastic biliary stents for one year, but metallic stents have increasingly been brought into use (86) .

The current study is the first RCT comparing multiple plastic stent therapy and cSEMS stenting in BBS caused by chronic pancreatitis. When conceiving the study, based on previous reports in the literature, management using cSEMS was assumed to be superior to that of multiple plastic stent therapy (18, 89) . However, according to the results both methods are highly efficient and superiority for either group could not be shown. However, the 95% CIs for the success rates are fairly wide, indicating the possibility that one of the methods is in fact better than the other.

The intended number for achieved 10 Fr stents in the NEPS group was six. This quantity was chosen to achieve a similar CBD diameter in both groups. Geometrically, six 10 Fr NEPS placed in a circle with a seventh stent in the center fills a 10-mm tube. In real-life stenting, a complete fit is impossible, which is why six stents can be considered close enough. Moreover, the spaces between the stents are thought to maintain drainage if the stents are clogged.

When using cSEMS, a two-staged procedure with one ERCP for deployment and another for removal is sufficient. As progressive stenting in the NEPS group required three ERCPs, a check-up ERCP between deployment and removal was included in the study protocol to eliminate the bias caused by unequal number of procedures.

As was the case in the post-LT cSEMS study, the optimal duration of stents was unclear when conceiving the CP study as well. The durations in anecdotal reports on cSEMS in BBS have varied, usually, however, being approximately 3 months (18, 19, 153) . On the other hand, progressive stenting with NEPS has typically lasted for one year, with the briefest stent duration being 6 months, as stent exchange and an incremental increase of stents are needed trimonthly (68, 88) . A 6-month duration was selected here, as at the time it was not known whether cSEMS coverage would remain intact for one year.

At present, it is known that cSEMS can be indwelled for up to one year, thus being an attractive option for stent therapy in CP. Six plastic stents require 2–3 ERCP procedures to change and increase stents to achieve an equivalent diameter,

and later additional procedures are needed to change occluded stents if a one-year stenting time is warranted.

No cost analysis comparing these stent therapies was conducted. However, a well-grounded assumption is that in clinical practice with a two-staged deployment-removal protocol for cSEMS the cost-structure would resemble that of the congruently studied post-LT patients in Kaffes' s et al (48). When summing the cost for nine plastic stents with two insertion catheters and one dilation balloon, it at least equals the price of one cSEMS, even without considering the cost of an additional ERCP procedure.

### **6.3 PREOPERATIVE BILIARY DRAINAGE (II)**

Historically obstructive jaundice has been considered to impair physical health prior to PD sufficiently to warrant surgical relief of the bile duct obstruction, resulting in a two-staged operation (120, 125, 154) . Naturally, when less invasive approaches via PTC- and ERCP-drainage became available, there was a shift towards their use (125) . In recent years, the need for preoperative drainage has been questioned and actually the current opinion is somewhat against routine PBD (1, 3, 100, 154) . The fundamental change in opinion came with a Dutch multicenter RCT published in 2010, showing a significantly lower risk for serious complications in jaundiced patients undergoing early surgery without PBD than in preoperatively stented patients(1). The complication rate related to the stenting procedure in that study was, however, high (46%), whereas the rates for actual postoperative complications showed no significant difference. In our study, the ERCP-related complication rate was 4.7%, with no severe complications. The low complication rate is probably explained by the high volum of ERCP procedures at our hospital, with highly specialized endoscopists. It should be noted, however, that the population for our study was gathered from surgical databases, and thus, there is a possibility of severe ERCP-related complications preventing an originally assigned surgery. The quantity of such patients logically cannot be very high, as such a scenario would have resulted in actions against PBD.

The issue of the choice between NEPS and SEMS has been investigated to a lesser extent. The substantially higher cost for SEMS speaks against its brief and temporary use during the preoperative course. The rationale against preoperative stenting is that it probably increases the risk for bacterial growth in the bile juice and some studies have shown this increases postoperative infection complications (127, 129) . It has been assumed that bacterial growth could be diminished if large-bore SEMS are used as they provide better biliary flow than NEPS. In this study there was no significant difference between the bacterial scores or the postoperative infection rates between the two stent types. The rate of infection complications in

stented patients versus UBO patients also did not differ. According to Kajiwara et al., a correlation exists between postoperative bacteria in the bile juice and Grade B and C postoperative fistulas (126). Neither the bacterial scores in our study nor the use of different stent types differed across the different fistula grades. However, all UBO patients had sterile bile, but as the number of UBO patients in this study was very small relative to stented patients, a significant difference in postoperative (infection) complications could not be established.

Interestingly, the Dutch group, which in 2010 published the RCT favoring early surgery over PBD, recently published a prospective cohort study comparing PBD with NEPS or fcSEMS and early surgery (124). It turns out the fcSEMS cohort was added to the earlier RCT, with the PBD-using-plastic stents cohort and the early surgery cohort as historical controls. The authors concluded the outcome for fcSEMS was better than that for NEPS in preoperative biliary drainage. However, as the PBD-related complication rate is very high in the historical PBD group, such a conclusion seems somewhat hasty. Furthermore, as the PBD was performed in different time periods, the superior results for fcSEMS may be the result of access to more evolved technical ERCP equipment and the endoscopists becoming more experienced and skilled over the years.

Even though cost-effectiveness for SEMS has been assessed in malignant palliative stenting, recently also for short-term stenting, no cost analyses have been conducted of plastic versus metallic stenting in preoperative drainage (6, 105). Currently, there are a few ongoing randomized trials comparing NEPS and SEMS in PBD; these probably are also assessing the costs (124).

Regarding bilirubin levels, more patients with NEPS than with SEMS reached levels below 20 and 50  $\mu\text{mol/l}$ . The differences were insignificant, although a trend towards superiority of NEPS was seen when the level was set to 50  $\mu\text{mol/l}$ . For both groups, the longer the time between stent placement and operation, the lower the preoperative bilirubin level. It is, on the other hand, possible that the SEMS affects the bile duct inducing ischemia or ductal hyperplasia impairing the bile flow.

#### **6.4 ENDOSCOPIC COVERED SELF-EXPANDABLE METALLIC STENT THERAPY IN BENIGN BILIARY STRICTURES IN PATIENTS WITH ALTERED ANATOMY (IV)**

The short length of the duodenoscope prevents its use in altered anatomy. Even if longer duodenoscopes were manufactured, it is unlikely they could be used, as advancement in the bowel would be difficult due to looping of the scope and its side-viewing quality. In recent years, device-assisted enteroscopes, such as DBE, have been used to perform ERCP in altered anatomy (137, 138). As standard ERCP devices are too short for DBE, short enteroscopes have been developed. The 2.8-mm



narrow working channel, however, limits the use of some appliances, e.g. SEMS (138-141) . The narrow channel also causes stress for the endoscopist; the pushing in and pulling out actions of the devices are very tight. Kawashima et al. compared instrument insertion time using a standard 2.8-mm working channel enteroscope with a prototype scope of the same length but a 3.2-mm-wide channel, showing faster insertion with the wider channel (148) . Thus, channel width obviously affects procedure time.

The long afferent limb in RYGB patients diminishes the success of reaching the papilla with short enteroscopes. Interestingly, several modifications of surgically or endoscopically assisted techniques entering the gastrointestinal (GI) tract through the remnant stomach have been developed (4, 146, 147) . These different approaches reflect the complexity and difficulty of performing ERCP in altered anatomy, especially in cases with a long Roux-en-Y limb.

Until now, through-the-scope placement of cSEMS using a long enteroscope has not been feasible due to the limited diameter of the working channel and the inappropriate length of the stent deployment catheter. Here we report the first case of fcSEMS deployment through the working channel of a long DBE. The stent was custom-made with a delivery device longer than those for standard fcSEMS. The DBE used has a 3.2-mm working channel, which is wider than that of other commercially available balloon enteroscopes. The properties of both endoscopes and accessories are evolving, improving the possibilities for endoscopic treatment of the pancreaticobiliary tract in patients with altered anatomy. There are also reports of a prototype short SBE with a 3.2-mm working channel (148, 149) . This endoscope enables the use of standard ERCP equipment including standard SEMS. Still, gaining access to the blind end may be challenging using a short scope.

In our two other cases, the patients had transcutaneous routes when admitted for DBE. Naturally, when this route exists, this advantage should be used to perform a rendezvous procedure. In fact, the HJ site would not have been reached in Case 2 without the existing PTC-route. A standard fcSEMS and delivery device can be inserted with the use of the transhepatic wire running along the endoscope. The advantage of using the rendezvous technique instead of a pure PTC technique is having the endoscopic view in addition to the fluoroscopic view.

Approximately one year after stent removal, the Case 2 patient suffered from cholangitis episodes due to hilar strictures. There was no sign of stricture on the stented HJ site, and the stent did not reach the hilum, and thus, it is not a case of stent-induced de novo stricture. A recently published German study on liver-transplanted PSC patients showed that 28% of the patients developed nonanastomotic biliary strictures, with or without concomitant anastomotic stricture, in their transplant (155) . Recurrent PSC was seen in 20% of the patients. Benign strictures, irrespective of the indication for LT, have previously been found in 5–15% of patients after

deceased donor LT (76) . Hence, the strictures and cholangitis episodes of this patient may be associated with PSC and/or LT.

### 6.5 STENT-RELATED DRAWBACKS (I, II, III, IV)

The main downside for NEPS is their clogging in approximately 3-4 months. As strictures usually need a longer stent duration than this, stent exchange is necessary.

Covered SEMS, again, are prone to migrate in up to 40% of cases(14). When the fcSEMS in our post-LT AS study were placed intraductally above the papilla, only one stent (4%; 1/24) migrated in 6% (1/18) of these patients. The cSEMS in the CP study also had a fairly low migration rate, (7%), although placed across the papilla. Upon retrieval, one Allium™ stent unravelled and one CP cSEMS broke. Furthermore, one CP cSEMS needed insertion of a cSEMS inside to enable removal and two were surprisingly broken prior to removal, a circumstance we could not explain. In patients with altered anatomy, stent migration could be desirable, provided it does not occur too soon after deployment. In Case 3 the patient had a plain X-ray to assess whether or not the stent was in place. This way, if migration occurs, one laborious and time-consuming DBE ERC could be avoided.

When cSEMS were first brought into use, there were concerns that the coverage would impair or occlude drainage of the cystic duct and the main pancreatic duct causing cholecystitis and pancreatitis, respectively. In LT patients, the gallbladder is removed, allowing the cystic duct to be traversed without concern. In the CP study, there was one acute cholecystitis in both stent groups. Both studies had only one case of mild PEP, and thus, neither cholecystitis nor pancreatitis appears to be an impending risk linked to the use of cSEMS.

Development of de novo strictures following stent therapy with cSEMS has been discovered(15, 21). It is likely that cSEMS, especially with high radial force, damage the bile duct epithelium to some extent. The clinical impact of this remains unclear. In our study, de novo strictures were not seen; however, neither were they sought. If there is a need for verifying or ruling out this entity, future ERCP reports should include exact measurements of the stricture length and its relative to the papilla, and in cases of recurrent or new strictures, the site of the previous stent must be known.

### 6.6 ASPECTS TO CONSIDER FOR CHOICE OF STENT (I, II, III, IV)

When choosing between stents, SEMS should clearly be preferred in malignant cases with a life expectancy longer than 4–6 months (6, 104) . The choice of cSEMS versus uSEMS in malignant strictures is, in turn, less clear. The main drawback with



cSEMS is migration, which diminishes both cost-effectiveness and the advantages of SEMS relative to NEPS.

Even more ambiguous is the choice of stents in BBS. Perhaps endoscopic therapy for BBS should be customized for every patient according to the stricture location, etiology, length, duration and special features like fibrotic firmness. Both multiple progressive plastic stenting and management with cSEMS appear to be efficacious in BBS, as shown in Study III, and patient comfort and probably also cost-effectiveness speak in favor of cSEMS. When choosing the cSEMS, endoscopists need to know and understand the features of the stent regarding radial and axial forces, possible antimigratory attributes and whether to place the stent across or above the papilla. Thus, it is probably best to know well a few carefully selected cSEMS with different features, acquiring experience with them in clinical use, rather than having numerous different types of stents available.

## **6.7 LIMITATIONS AND STRENGTHS OF THE STUDY**

Study I is limited by its retrospective nature and the small number of patients. The results were also not compared with historical stent therapy with NEPS, as this group of patients was previously managed outside our unit. The study can be considered as a descriptive pilot project to determine outcome using this type of stent in post-LT AS. Indeed, our unit is currently participating in a multicenter study comparing multiple NEPS therapy with cSEMS therapy in this patient group. The multicenter setting is crucial, as the number of LT patients with AS in individual ERCP units is fairly small.

The great discrepancy in the number of patients between groups in study II biases the results, and affects the possibility of detecting statistically significant differences between the groups. Moreover, the study is of retrospective character and covers a long time period, and thus, other changes in the treatment protocol of operated patients can also have an impact on the results. Because the patients were gathered from a database of PD- or TP-operated patients, the possibility exists, that stented patients with severe PBD-complications preventing surgery were missed. However, the great number of NEPS patients together with their results gives some confidence that NEPS is a good alternative for PBD.

A bacterial score was invented in order to assign a numerical value for the bacterial strains and the amount of bacteria cultured from the bile juice. This score is not validated in any way. Moreover, it does not consider the virulence of the strains cultured.

The prospective RCT design of Study III is a definite advantage, especially considering the fact that no previous studies comparing multiple NEPS and SEMS in this setting have been published. However, when conceiving the study, the power

calculations were based on the contemporary belief that cSEMS would be superior to NEPS. Surprisingly, the different managements did not differ in outcome; a larger population might have revealed significant differences. The recruitment of patients took five years, and an increase in patients would probably require an international, multicenter study. As the centers taking part in the study were of different sizes, the distribution of the recruited patients was skewed. This study was also limited by the lack of cost analysis.

Limitations of Study IV include its case report nature and the low number of cases. A strength, again, is the endoscopic placement of fcSEMS, which has not previously been described using a long DBE in this patient group. Additionally, the detailed description of the procedures and the equipment used facilitates adaptation of the technique by interventional endoscopists worldwide.

Three or four interventional endoscopists performed the procedures in Studies I and IV, and the majority of the procedures in Studies II and III. Thus, the results can be biased by personal preferences. On the other hand, the limited number of endoscopists diminishes the diversity of the differences in experience and skills that a large pool of endoscopists would entail. Furthermore, the outcome of the procedures was mainly evaluated by the endoscopists themselves, possibly affecting the interpretation of the procedures.

## 6.8 FUTURE PERSPECTIVES

The field of stent therapy is continuously evolving, not only regarding the stents but also other equipment needed. Improvement of the stents with respect to patency, functionality, and removability along with advancement in stent therapy methods, are current hot topics.

Magnetic tipped plastic stents, providing for removal without repeat ERCP have been tested in animal models(8). The stents were removed under fluoroscopic control using an external magnet. The authors expressed concern regarding proximal migration of the stent inside the duct with improper handling of magnets. Another consideration is what would happen if the patient for some reason needs an MRI. Hence, further studies are needed for this technique.

Compared with the above, biodegradable stents form a more feasible alternative to avoid ERCP for retrieval of the stent, not least as there has already been experimental, successful human use(34). A future topic of study is whether debris following degradation forms a problem. Biodegradable stents appears to be an especially useful alternative in patients with altered anatomy. An intriguing future option is combining biodegradable stents with drug-eluting qualities. Shi et al. conducted an in vivo study on dogs using paclitaxel-coated supporting PLA stents when performing a cholangiojejunostomy to prevent BBS (156) . They showed that

paclitaxel significantly inhibited myofibroblast activation and proliferation and also excessive collagen deposition in the bilioenteric anastomosis. Moreover, the biodegradable polymer material seemed applicable in the controlled release of the drug. Finally, because paclitaxel has been used in coronary stents for decades, its use has gained trust (157) .

Despite similar surgical trauma, some patients will sustain abundant adhesions, while others will not. This is probably linked to the patient's tissue type. In the future, maybe, susceptible tissue types can be identified, allowing the use of stents coated with drugs (such as paclitaxel) to reduce scar formation at surgical anastomoses or to prevent restenosis after stent therapy in patients more prone to form scar tissue.

Other drug-eluting and radioactive properties appear to offer stent therapy endless possibilities, especially in the treatment of malignant strictures (36, 37).

Furthermore, ERCP equipment and supplementary devices needed in DAE ERCP will likely improve and evolve as their demand increases.

## **6.9 GENERAL ASPECTS**

The subject of this thesis, although versatile, forms only a limited part of endoscopic management of the pancreaticobiliary tree. Interventional endoscopists must not only acquire skills to perform the complex procedures, knowledge about the techniques, equipment and devices, but also deep insight into numerous diseases, postoperative states and their etiologies and pathophysiologies. Hence, it is clearly advantageous to centralize this kind of management. The research in this field is active, resulting in rapid evolution of equipment, devices and techniques. However, managing all technically possible biliary states using ERCP is not always gaining the patient.

## 7. SUMMARY AND CONCLUSIONS

The use of SEMS in extrahepatic biliary strictures is experimental and unclear. The following conclusions can be drawn from this study:

- 1) Anastomotic complications after LT can be efficaciously and safely managed using cSEMS, especially if placed intracholedochally. The duration of stent therapy and the stent types need further assessment.
- 2) Compared with SEMS, preoperative stenting with NEPS appears to produce sufficient biliary drainage.
- 3) Six months of stent therapy, either with cSEMS or progressive multiple stenting with NEPS, is safe and efficacious in bile strictures caused by CP. Treatment with cSEMS adds to patient comfort and is probably cost-effective as well.
- 4) Evolution of double-balloon enteroscope properties and delivery devices enables endoscopic deployment of cSEMS in BBS in patients with altered anatomy. If the patient has preceding PTC, this route can be used for rendezvous procedures.
- 5) The ERCP-related complication rates are low in a high volume ERCP center.

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